# American Heart Journal

*An international publication for the study of the circulation*

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*VOLUME 72*

*JULY DECEMBER 1966*

# American Heart Journal

JULY 1966




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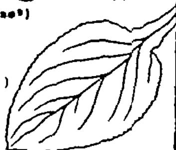
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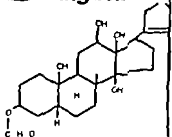
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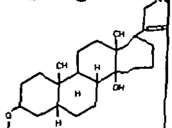
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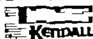


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**One thing two generations of physicians have in common**

**Dilaudid (hydromorphone) – still unmatched for analgesic action**

In my experience most patients vomit after receiving morphine and I have usually substituted Dilaudid which causes vomiting much less frequently Dilaudid is a synthetic drug related to morphine with proportionally more analgesic and less soporific and respiratory depressant effect

Friedberg C K Diseases of the Heart ed 2 Philadelphia, W B Saunders Co [illegible] p [illegible]

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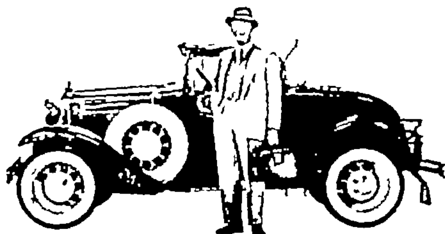
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Friedberg C. K. Diseases of the Heart ed 2, Philadelphia W B Saunders Co 1956 p 171

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Vol 72 No. 2 August 1966 American Heart Journal published monthly by The C V Mosby Company 3207 Washington Boulevard St. Louis Mo 63103 Second class postage paid at St. Louis, Mo and at additional offices. Subscription rates United States and Its Possessions $14.00 Canada, Latin America and Spain $15.00 Other Countries $15.50 Students, interns and resident physicians United States and Its Possessions $8.40 Canada, Latin America, and Spain $9.00 Other Countries $9.90 Single copies $2.00 postpaid Printed in the U S. A. Copyright © 1966 by The C V Mosby Company

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Friedberg, C. K. Diseases of the Heart, ed. 2, Philadelphia, W. B. Saunders Co. [illegible] p. [illegible]

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V[illegible] 72, No. 4, October 1966. American Heart Journal is published m[illegible]ly by The C. V. Mosby Company, [illegible] Washington Boulevard, [illegible] Louis, Mo., 63103. Second-class post[illegible] paid [illegible] Louis, Mo., and [illegible] offices. Subscription [illegible] United States and [illegible] Possessions $14.00; Canada, Latin America, and [illegible] $15.00; Other Countries $[illegible] [illegible] interns, and resident physicians: United States and [illegible] Possessions $8.40; Canada, Latin America, and [illegible] $9.40; Other Countries $9.90 [illegible] $3.00 postpaid. Printed in the U. S. A.

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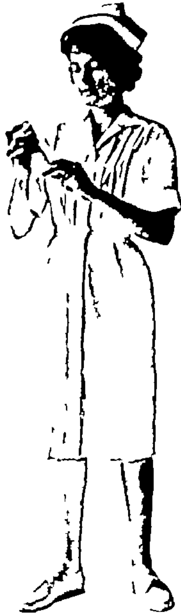


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**One thing two generations of physicians have in common**

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Friedberg, C. K.: Diseases of the Heart, ed. 2, Philadelphia, W. B. Saunders Co., 1956, p. 871.

# DILAUDID®
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Vol. [illegible], No. 5, November 1966. American Heart Journal is published monthly by The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo. 63103. Second-class postage paid at St. Louis, Mo., and additional mailing offices. Subscription rates: United States and Its Possessions $14.00; Canada, Latin America, and Spain $17.00; Other Countries $17.00 [illegible] interns, and residents [illegible] physicians: United States and Its Possessions $4.40; Canada, Latin America, and Spain $9.40; Other Countries $9.90 [illegible] copies $2.50 postpaid. Printed in the U. S. A.

# American Heart Journal

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# a built-in safety factor in digitalis therapy for geriatric patients



Elderly patients are more prone to overdigitalization and toxicity The zone between digitalization and digitoxicity becomes narrower with advancing age

Smooth maintenance is possible with the use of *powdered leaf digitalis* Overdosage or intolerance with *powdered leaf digitalis* is usually signalled by anorexia nausea and vomiting diarrhea or visual disturbances a built in safety factor to help avoid serious cardiac arrhythmias These traditional warnings are often absent when certain purified crystalline preparations are utilized

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DOSAGE [illegible]

CAUTION [illegible]

AVAILABILITY [illegible] bottle of 100

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Vol 72 No 6 December 1966 American Heart Journal published monthly by The C. V. Mosby Company 3207 Washington Blvd St. Louis Mo 63103 Second class postage paid at St Louis, Mo [illegible] United States [illegible] Possessions $14.00 Canada Latin America and Spain $1[illegible]00 Other Countries $1[illegible] Students interns and resident physicians United States and Possessions $8.40 Canada, Latin America and Spain $9.40 Other Countries $9.90 Single copies $1.50 postpaid Printed in the U.S.A.

# *Behind continued high blood pressure readings lies the possibility of organic damage*[1-13]

MANY OF THE aspects of essential hypertension are unpredictable — either because there are a number of me hanisms involved or because individ uals differ in their responses to these mechanisms [1]

There is one aspect of hypertension however that seems in many cases predictable when the blood pressure is elevated to a marked degree for an adequate period of time this in itself leads to per petuation of the syndrome with resulting vascular damage throughout the body [14] All too often the disease progresses until there is damage to one of three vital organs the heart, the kidney the brain

Hypertension is certainly a major factor in the genesis of coronary heart disease and it is even more important when compounded with obesity [4]

[Vascular deterioration] can be clearly seen in the kidney with a degree of damage that can be meas ured by renal function studies [10]

most evidence suggests that reduction of blood pressure when it is too high not only relieves the heart of excess work but reduces vascular damage [1]

In short treatment is indicated [1]

Antihypertensive therapy will not restore the blood vessels to normal Yet many of the vascular changes and symptoms caused by increased blood pressure may be arrested or alleviated when the blood pressure is reduced to normotensive levels [7]

Reducing the blood pressure helps curtail further vas cular damage and improves the prognosis — when damage is not too far advanced before therapy is started [14] Essential hypertension is an indication not only for treatment but for early and adequate treat ment of the patient in question

Reduce the blood pressure with Rautrax N
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For most patients 1 or 2 Rautrax N tablets daily are sufficient for maintenance therapy The simplicity convenience and e onomy of such a dosage schedule are of particular benef t to older patients

References 1 Page I H and Dustan H P The Usefulness of Dr gs in The Treatment of Hypertension in Ingelfinger F J Relman A S and Finland M Controversy in Internal Medicine Philadelphia W B Saunders Co 1966 p 95 2 Hi [illegible] W The [illegible] of Art Hypertension Therapy of Essential Hypertension [illegible] Relman, A S and Finland M Controversy in Internal Medicine Philadelphia W B Saunders Co 1966 p 97 3 Moyer, J H An Hypertensive Agents and the Drug Therapy of Hypertension in Goodman L S and Gilman A The Pharmacological Basis of Therapeutics ed 3 New York The Macmillan Co 1965 p 727 4 [illegible] D M Ind [illegible] Med & Surg 32 371 1963 5 Cohen B M [illegible] 91 645 1963 6 Lee R E et al Am J Cardiol 11 718 1963 7 Moyer, J H Am J Cardiol 9 8 1 1962 8 [illegible] New York J Med 62 1177 1962 9 Wood J E and Battey L L Am J Cardiol 9 675 1962 10 Moyer J H and Heider C Am J Cardiol 9 920 1962 11 Moser M and McCarthy A New York State J Med 60 679, 1960 12 Ardson W E Nebraska M J 44 305 1959 13 Hodge J V McQueen E G and Smirk H Brit M J 1 5218 1961 14 Moyer J H and Brest A N Hypertension Recent Advances Philadelphia Lea & Febiger 1961 p 633 15 Berry R L and [illegible] H P J Am Geriatrics Soc 10 816 1962 16 Reid W J J Am Geriatrics Soc 13 365 1965 17 Feldman L [illegible] J 23 248 1962

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Dosage and Supply Initial dosage 1 to 4 tablets daily [illegible] Maintenance 1 or 2 tablets daily Rautrax N [illegible] as capsule shaped tablets containing 50 mg Raudixin (Rauwolfia serpentina whole root) 4 mg bendroflumethiazide (Naturetin) 400 mg potassium chloride Also available Rautrax N Modified — capsule shaped tablets containing 50 mg Raudixin (Rauwolfia serpentina whole root) 2 mg bendroflumethiazide (Naturetin) 400 mg potassium chloride Both potencies available in bottles of 100 For full information see Product Brief

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American Heart Journal

*July 1966 Volume 72 Number 1*

# Editorial

## Some aspects of circulatory and respiratory functions in mammals

*H. Bartels, M.D.**
*Tübingen, Germany*

> On peut faire de grands progrès avec une théorie fausse.
>
> Claude Bernard

Studies in comparative physiology can open to the physician new aspects which, although he has often read that page in the book of nature concerning Man, have previously gone unnoticed. Suddenly he sees how fantastically diverse are the possibilities provided by nature, for example, the ability of animals to satisfy their varying metabolic rates. Even consideration of this problem within the framework of the rather homogeneous class Mammalia furnishes one with amazing insight.

With the exception of his mental prowess, Man is a rather average mammal. His body weight is 10,000 times greater than that of the smallest mammal, yet the elephant weighs 60 times more and the large blue whale weighs 2,000 times more.

As we learn from mathematics, one can often derive an understanding of relationships better by observation of extreme cases. Therefore, we will focus our attention preferably upon the very small and very large animals.

Unfortunately, physiologic measurements on both extremely large and extremely small animals are fraught with methodological difficulties of all types. Measuring the cardiac output of a 12 gram shrew seems at present to be an almost impossible undertaking. Likewise, the insertion of a heart catheter into a 5 ton unanesthetized elephant could become a dangerous venture should the animal, with his agile trunk, interest himself in the procedure or, even worse, in the operator. Nevertheless, my friends Cecil Luck and Peter Wright in Uganda succeeded in measuring the cardiac output in immobilized African elephants. But, normally, information that can be obtained from these extreme animals is limited to procedures which can be more simply carried out, such as the obtaining of morphologic data from dead animals and the measuring of metabolic rate and blood function, which are meaningful to any studies of respiration and circulation.

The remarkable investigations performed by Francis G. Benedict in the nineteen thirties in Washington, D. C., on the 3.5 ton Indian elephant "Jap" remain a famous example of this type of research. Benedict found the basal 24 hour production of heat of "Jap" to be 50,000 calories, equal to that of 30 men. Per kilogram of body

*[illegible]
[illegible]

weight the elephant produces 13 calories whereas the human being produces approximately 26 calories in 24 hours. This shows a lower metabolic intensity in the elephant than in Man.

On the other hand, a shrew produces 0.005 calories per minute, which is equal to 0.5 calorie per kilogram of body weight or more than 700 calories per kilogram in 24 hours.

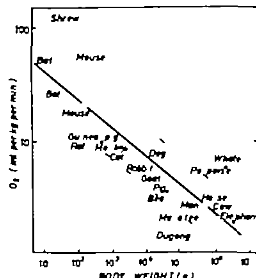



Fig. 1 Metabolic rate (milliliters of oxygen per kilogram per minute) as a function of body weight. (From Bartels: Lancet, p. 599, 1964.)

Fig. 1 illustrates the increasing metabolic activity with decreasing body weight. Instead of the production of heat, the consumption of oxygen is used as a basis of comparison. This figure demonstrates the fact known as the *law of diminishing metabolism*.

The mere establishment of a biologic law is of course not an explanation of cause. To date no satisfactory theory has been advanced to explain this phenomenon. Conversely, the fact of the matter alone drives the biologist in the pursuit of answers to some very exciting questions, for example, how the varying metabolic demands are met by the various species or, restricting the topic, how the "call for oxygen," as expressed by August Krogh,[4] is met.

Lung volumes and heart weights have been found to be linearly related to body weight in mammals (Fig. 2). Thus, morphologically speaking, we do not find any sign of adaptation to metabolic rate in the various species investigated. A linear relationship of tidal and stroke volumes

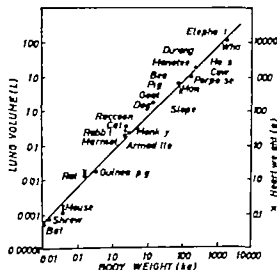



Fig. 2 Logarithmic plot of lung volume and heart weight as a function of body weight. Data on lung volumes from Tenney and Remmers; data on heart weights from Spector. Heart weights are represented by crosses.

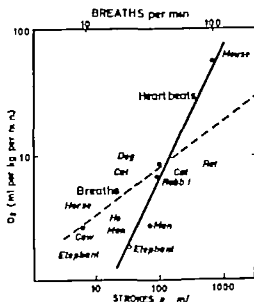



Fig. 3 Metabolic rate (milliliters of oxygen per kilogram per minute) as function of frequency of respiration and the heart, respectively. (From Bartels: Lancet, p. 599, 1964.)

to body weight would mean that if alveolar ventilation and cardiac output were sufficient for the elephant they would be too low to meet the metabolic demand of the shrew. Respiration and heart rate provide an explanation increasing with decreasing animal size (Fig. 3). This suggests that ventilation and cardiac output are more closely related to the metabolic rate than to the body weight.

Greater ventilation and perfusion in the lung do not, however, necessarily mean that more oxygen is taken up by the blood. The diffusion surface of the lung could be too small, that is, the diffusion capacity could still be insufficient for the metabolic demands. Tenney and Remmers[14] have actually found that small animals possess alveoli which are smaller than those of large animals. This means that the total alveolar surface available for gas exchange is greater in small animals than in large animals. As a result of these increased diffusion areas relatively more oxygen and carbon dioxide can diffuse per unit of lung volume in small animals, thus enhancing the intake of oxygen.

The increased amount of oxygen taken up in the capillaries of the lungs of small animals can perhaps be properly transported to the tissues by means of the relatively high cardiac output alone, but this is somewhat uncertain. In Fig. 4 the results of several measurements, probably not all of which are reliable, are plotted together and indicate this basic principle. However, because of the unreliability of the measurements it is nonetheless difficult to say with any degree of certainty whether this is true. If cardiac output alone does not suffice to transport the increased quantity of oxygen, then other mechanisms should make themselves evident, reflected in the transport characteristics of the blood, unless we have a complete théorie fausse.

A glance at the hemoglobin concentration (grams per 100 milliliters of blood) does not show any reasonable relationship to body weight. However, special characteristics of hemoglobin favoring the uptake of oxygen in the lung as well as the giving off of oxygen to the tissues, illustrated by the well known oxygen dissociation curve, do show differences between large and small animals.

The unloading tension for oxygen can be characterized by the half saturation for oxygen in the blood. This value is on the average higher in small animals than in large ones. The extreme cases of elephant and shrew demonstrate how this change in unloading tension becomes advantageous to the small animal (Fig. 5).

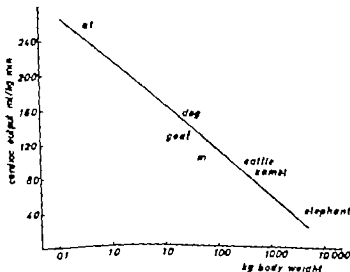



Fig. 4 Cardiac output (milliliters of blood per kilogram per minute) as a function of body weight. Data from Spector and for the African elephant from Luck and Wright.

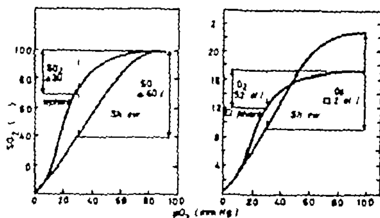



Fig. 5 Oxygen ... of the shrew and the ... (... Fed Proc ... p 539 1961.)

The blood of the shrew is 60 per cent de saturated at an oxygen tension of 30 mm Hg whereas the blood of the elephant is only 30 per cent desaturated. Further more the higher hemoglobin content of the shrew's blood results in a higher ar terial oxygen content. Thus all in all the shrew's blood at a tension of 30 mm Hg is able to give off 13 ml of oxygen to the tissues whereas the elephant's blood at the same tension can deliver only ml.

One sees now that in these two extreme examples of land dwelling mammals mech anisms also exist in the blood to support the increased need for oxygen.

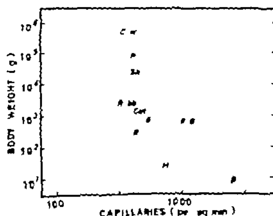



Fig. 6 Logarithmic plot of body weight as a func tion of capillaries per square meter in gastrocnemius muscle (data from Schmidt Nielsen and Pennycuik.)

August Krogh[a] postulated that the capillary density should reflect the call for oxygen. This meant that capillary den ity should be increased in small ani mals. Recent investigations by Schmidt Nielsen and Pennycuik only slightly support Krogh's belief (Fig. 6). These authors think that other variable factors such as domestication acclimatization to cold and the amount of physical activity were too different in the species studied to allow any clear-cut relationship to be determined. On the other hand I am in clined to believe that in so far as small animals are concerned the relatively in creased circulation and oxygen unloading capacity are of themselves sufficient to satisfactorily oxygenate the muscle tissue which is capable of almost complete de saturation. It is interesting to note in Fig. 6 that only the bat has a significant increase in capillary density. Of all the species investigated the bat alone is the only animal that is able to fly an ac complishment more strenuous than the other species are capable of.

Finally it has also been found that the cells of small animals have a much higher cytochrome oxidase activity and cyto chrome C concentration also furthering a higher turnover of oxygen within the tissues.

Now we have the impression that ven tilation cardiac output lung surface area oxygen unloading capacity as well as cell enzymes together meet the increased

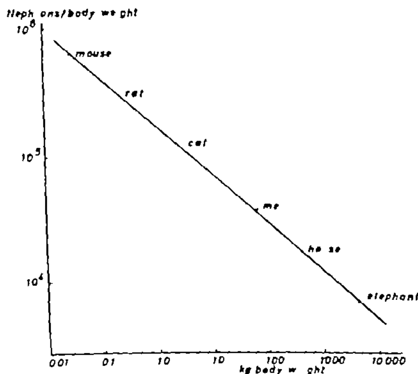



Fig. 7 Number of nephrons per kilogram of body weight as a function of body weight (data from Adolph).

demands of increased metabolism in small animals as compared with large animals. Of course this is only one aspect of the problem. It should also be expected that the resorption surface of the gut and the excretory surfaces of the kidney would show a relationship to metabolic rate. The number of nephrons lend support to this view, as Fig. 7 illustrates.

The question of why is there no larger land animal than the elephant is not answerable with any certainty, although mechanical problems must undoubtedly be among the limiting factors. The much larger brachiosaur is no counterargument because much evidence leads us to believe that it spent its life in swamps, thus utilizing the effects of buoyancy to support its great body in a manner similar to that employed by whales.[1] Also from the standpoint of metabolism it is difficult to conceive of any land animal exceeding the elephant in size, since according to reports he is forced to spend almost 20 hours per day in the consumption of about 500 kilograms of grass and leaves. Any significantly larger elephant would be forced, in spite of its innate reduction in metabolism, to spend 24 hours a day eating, thus requiring an even greater area in which to forage. To traverse this large forage area would alone require a vast expenditure of energy. Apparently heat regulation is also a limiting factor. Larger elephants or even present day elephants with a more intense metabolism would have great difficulty giving off the heat produced during muscular activity. The large ears of the elephant are actually special radiators which serve the process of heat regulation and would have to increase greatly in size. It is perhaps no coincidence then that African elephants, which are larger, have larger ears than their smaller Indian counterparts.

Perhaps the question of why there is no smaller mammal than the pygmy shrew can also be partially satisfied with the same answer applied to elephants. These minute mammals, which have a body weight of about 3 grams, must like the elephant also forage practically all night and day. The metabolism of these animals could not actually be reduced since they must

# Clinical communications

## The "late systolic heartbeat" of pericardial effusion

*Calvin F. Kay, M.D.**
*Claude R. Joyner, M.D.*
*John Helwig, Jr., M.D.*
*Thomas F. Raymond, M.D.*
*Philadelphia, Pa.*

Several abnormalities of auscultation and palpation have been described in association with pericardial inflammation, effusion, constriction, or calcification. Of these, only three, in so far as we are aware, are systolic phenomena: reduction in intensity of the heart sounds and of the apex impulse, systolic friction rubs and clicks, and the systolic retractions that precede the diastolic heartbeat of constrictive pericarditis. We have recently observed a patient with chronic pericardial effusion in whom a loud sound and early palpable thrust were present late in systole. We believe that the mechanisms responsible for the production of these related phenomena bear some resemblance to those responsible for the pericardial knock,[3] frequently observed in the era of therapeutic pneumothorax, in which the hypermobile heart, suspended in air, bumped against the precordium in systole.

The patient, a 56 year old woman employed as a cashier in a cafe, was initially examined at the Hospital of the University of Pennsylvania in March 196 . She had had transient episodes of palpitation and tachycardia, documented to be attacks of paroxysmal atrial fibrillation, for many years. She also described many episodes of sharp pain, rarely lasting more than a few seconds, located in various areas of the anterior chest, unrelated to exertion, but possibly aggravated by breathing. These had been present from time to time for about 10 years and were at times so severe that she was hospitalized with suspected coronary occlusion on two occasions. The onset of her chief symptom, excessive fatigue with mild exertion, was difficult to date. It may have been present for 2 or 3 years, but had been a serious handicap to her activities for about 6 months. Some sense of breathlessness was occasionally noted. She had never had cough, orthopnea, or edema. A soft basal systolic murmur was first observed in 1954. An x-ray film taken at that time was reported to show slight cardiac enlargement, which was again noted in films in 1957 and 1961. Another film, taken Jan. 19, 1965, showed a large heart shadow, and this persisted despite digitalis and diuretics. Examination on March 1, 1965, revealed a slender woman of 56 years. The blood pressure was 108/70 mm. Hg with no paradoxical change with respirations. The lungs were clear, the neck veins and liver were not engorged, and edema was not present. As indicated by percus-

[illegible] of the Department of Medicine, University of Pennsylvania, Philadelphia, Pa. [illegible] supported [illegible] HE-0[illegible] HE-0[illegible] and HE-0[illegible] from the [illegible]
[illegible] Sept. [illegible] 1965.
Received for publication [illegible] University of Pennsylvania, 3400 Spruce St., Philadelphia, Pa.
*Address [illegible]

ion the heart was quite large. Well inside the left border a sharp thrust could be felt. This was originally identified as the apex impulse, but it was further inside the left border than would be expected. On auscultation it was immediately noted that this thrust coincided with a very loud sound that seemed to be in time but not in location the first component of a widely split second sound. It could barely be heard at the base and was alternately very loud and relatively soft in successive beats with considerable regularity. When breathing was suspended this alternation disappeared and the sound was relatively soft with each beat. The first and second sounds were easily heard but not loud and a faint systolic murmur was audible in the pulmonic area.



Fig. 1. Chest x-ray film of the patient, March 2, 1965.

In an effort to diagnose the nature of the patient's illness and mechanisms responsible for the unusual auscultatory findings, a number of additional studies were carried out. The blood count, serologic tests, urine analysis, serum electrolytes, and a series of lupus erythematosus preparations were normal or negative. The chest x-ray film (Fig. 1) showed generalized cardiac enlargement. On fluoroscopy with image intensification the cardiac shadow was almost motionless but a mass with ill defined limits could clearly be seen to move actively within the central portion of the total cardiac shadow, confirming the suspicion that a pericardial effusion was present. This was further confirmed by a

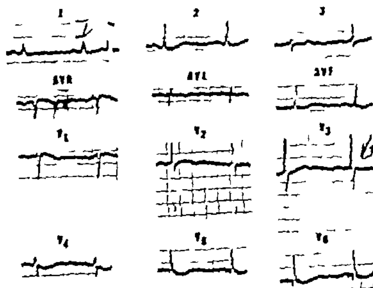



Fig. 2. Electrocardiogram, March 2, 1965. Abnormalities compatible with digitalis therapy.

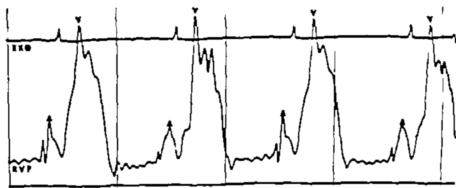



Fig 3 Right ventricular pressure Large A waves with alternation of A and of V pressure curves




Fig 4 Triple contour of ultrasound (*UKG*) record of anterior leaf of mitral valve (*M* $M_2$ $M_3$) Mitral opening (*MO*) and closure (*MC*) Prominent A wave systolic retraction (*SR*) and late systolic thrust of apexcardiogram (*ACG*) Systolic sound (*Sx*) at onset of rapid outward movement of systolic thrust Alternation of all components except *EKG*

radioisotopic scan and by ultrasound The electrocardiogram showed some RST depressions that could be ascribed to the digitalis which she had been receiving The amplitudes of all electrocardiographic components were normal (Fig 2)

On right heart catheterization oxygen saturations were all normal with no evidence of shunts Right ventricular systolic and diastolic pressures were mildly elevated (40 7 mm Hg) as was the pulmonary arterial pressure (40/15 mm Hg) A prominent A wave was present in the right ventricular pulse curve (Fig 3) A dye-dilution curve (superior vena cava to left brachial artery) confirmed the absence of a shunt The cardiac index was calculated at 1 99 L /min /M² markedly reduced from the normal of 3 25 ± 0 25 Two selective cineangiocardiograms were obtained These confirmed the presence of a pericardial effusion The left atrium ap

peared to be a little enlarged but otherwise no structural abnormalities were defined. Active contraction of the ventricular chambers was apparent.

Simultaneous recordings were then made of the heart sounds and apexcardiogram (ACG) (recorded from the point of maximum thrust inside the apex of the heart shadow) together with the ultrasonic cardiogram (UCG) and the electrocardiogram (ECG) (Fig. 4). The alternating beat to beat variations are obvious in all except the ECG which remains unchanged. The extra sound Sx is in mid to late systole with the timing varying slightly on various tracings, a phenomenon which

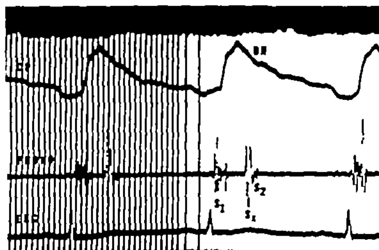



Fig. 5. Carotid pulse (*CP*) with dicrotic notch (*DN*) immediately preceded by $S_2$.

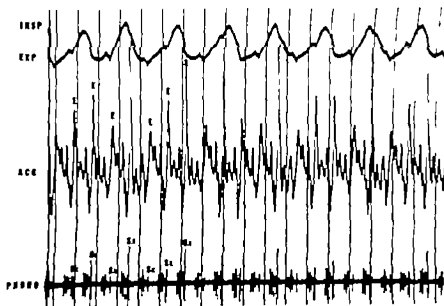



Fig. 6. Loud *Sx* and large apex thrust (*E*) in late inspiration and early expiration. Faint *Sx* and small apex thrust (*E*) after expiration and in early inspiration.

has also been noted previously with the pericardial knock. The first heart sound which precedes the large Sx is louder than in the beats in which Sx is small. Sx, large or small, is seen to occur during the sharp rise in outward thrust of the chest wall. The duration of outward thrust is longer in the large Sx beats than in the small ones. The UKG beamed on the anterior leaf of the mitral valve shows coincidence of the closure of the valve (MC) with the first sound as is normal. Mitral valve opening (MO) follows S by a normal interval. During the period of diastole the triple movement of the valve ($M_{1,2,3}$) resembles that found by one of us (C.J.) in various disorders associated with decreased ventricular diastolic compliance.

In subsequent records $S_2$ was found to slightly precede the dicrotic notch of the carotid pulse curve as expected (Fig. 5). Additional studies (Fig. 6) showed that the intensity of Sx and of the associated precordial thrust correlated directly with the phase of respiration. Maximum intensities were at the peak of inspiration or on the downslope of expiration, and minimal intensities occurred at the end of expiration or during the early rise in inspiration. This confirmed earlier clinical observations. By a coincidence in most of the recordings the resting respiratory rate was consistently very near to half the pulse rate. The respiratory effect is visible in the alternate variations of the A waves of the right ventricular pressure curve, the variations during late diastole in the apexcardiogram, and in the UKC, and probably in the variations in intensity of $S_1$.

Because the tuberculin test was very strongly positive in lowest dilution, it was decided to employ a therapeutic trial of antituberculous drugs. After 1 month the patient returned to the hospital, her symptoms and findings unchanged. A thoracotomy was then performed by Dr. Gordon Danielson. The pericardium was slightly thickened and contained about 900 c.c. of hazy straw-colored fluid. The anterior pericardium was removed, and the patient recovered uneventfully. Sections of the pericardium were reported to show a nonspecific pericarditis, and cultures of the tissue and fluid showed no evidence of tuberculosis or other infectious agent. Postoperatively, the unusual sound had disappeared. Several of the studies were repeated. The apexcardiogram, heart sounds, and UKG of the mitral valve movements were now all normal (Figs. 7 and 8).

It is concluded that the systolic thrust and related loud late systolic sound were

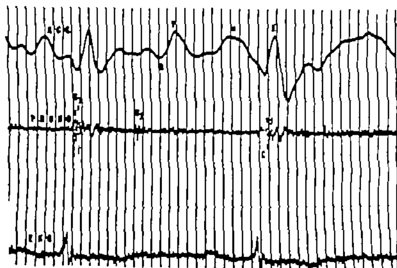



Fig. 7. Postoperative disappearance of Sx and relatively normal ACG.

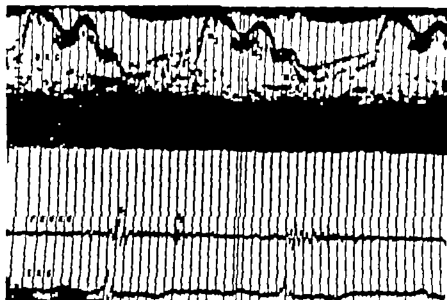


Fig. 8. Postoperative PKG of anterior leaflet of mitral valve. The abnormal middiastolic anterior deflection ($M_2$) is no longer seen.

the result of a forward thrust of the heart suspended in fluid against the overlying pericardium and that in turn against the chest wall. The remarkable degree of variation in these related phenomena with respiration suggests the possibility that as the anterior pericardium is drawn down by the descending diaphragm the heart is brought closer to it in a better position to strike it during systole. This could also account for the increased intensity of the first sound. However, the respiratory variation in the atrial filling wave and the change in the systolic pressure curve in the right ventricle suggest that the increased intensity of these phenomena relate rather to increased right ventricular filling during inspiration. This combination of thrust and sound must not of course be confused with the diastolic heartbeat described by Skoda[3] in 1852 which Wood[4] recognized *to be the result of the forward* thrust of the heart propelled by a high venous pressure through an anterior window of an otherwise constrictive pericardium. This sound could hardly be confused with a systolic click or a friction rub. The mechanism bears some analogy, as noted above, to the sound and thrust of the "pericardial knock" of pneumothorax and also to the late systolic sound and thrust rarely observed as a result of the paradoxical movement of the scar of an apical aneurysm. That this late systolic thrust and sound is not a common observation in pericardial effusion seems to be surprising, but our experience has been that it is not.

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# Systemic scleroderma with complete heart block

## Report of a case with comprehensive study of the conduction system


*Maurice Lev, M.D.*
*Milton Landowne, M.D.*
*Joseph C. Matchar, M.D.*
*John A. Wagner, M.D.*
*Chicago, Ill., and Baltimore, Md.*


Involvement of the heart in generalized scleroderma is well known[1-3] and the occurrence of various arrhythmias in this disease has been documented. However, few cases of complete heart block in generalized scleroderma have been reported in the literature.[4-9] In none of these was extensive study made of the conduction system. This report presents a clinical study of a patient with generalized scleroderma who developed complete heart block under observation; a comprehensive study was made of the conduction system at autopsy.

### Clinical review

This 49-year-old married baker, native born of Italian ancestry, was well until September 1953 when he developed swelling of his hands, weakness, left eye, shoulder pain, stiffness of the back, anorexia, and loss of weight of 10 pounds. There was no preceding history of recognized infection or of drug usage. The family and social histories were noncontributory. Examination revealed some swelling of the hands, pallor, and tightness of skin over the fingers. He was hospitalized for evaluation 1 month later (Lutheran Hospital, Baltimore) with the additional symptoms of pain in the interphalangeal, wrist, and elbow joints and swelling of both wrists and interphalangeal joints with tenderness and pain on motion of the elbow, knees, and ankles. The heart was not enlarged, no murmurs were heard, and the blood pressure was 110/68 mm. Hg. Laboratory studies showed an eosinophilia of 7 to 10 per cent. Blood uric acid was 5.7 mg. per cent. Preparations for lupus erythematosus cells were negative. There was no urinary protein nor Bence Jones protein. X-ray films of the involved joints and of the chest were negative, and the cardiac borders showed no enlargement. Examinations of the esophagus, stomach, and colon after the administration of barium were also normal. An electrocardiogram showed a sinus rhythm with normal A-V conduction. P-R was 0.16 second, QRS was 0.08 second, and Q-T was 0.36 second. The frontal axis of P was nearly vertical (between 60 and 90 degrees). QRS was small; a broad S was most prominent in Lead II but discernible in Lead I, indicating a low terminal component directed headward and to the right at about 240 degrees (−120 degrees) and opposite to the initial deflection of a narrow frontal loop. T was small, and in the precordial leads it was isoelectric in Lead V. The terminal QRS abnormality, although not then considered to be clinically significant, presaged the disorder to come.

From the C[illegible] Heart Disease Research [illegible] Training Center, [illegible] Medical Research [illegible] the Department [illegible] of [illegible] University Medical School, University of Chicago School of Medicine [illegible] University of Illinois College of Medicine, Chicago, Ill.; the [illegible] [illegible] Lutheran Hospital of Maryland [illegible] Department of Medicine [illegible] Johns Hopkins University and University of Maryland School of Medicine, Baltimore, Md.


This research was supported by Grant [illegible] H-3440 and HE-[illegible] from the National Heart Institute, [illegible] of Health, Bethesda, Md.

Received for publication Sept. 7, 1965.



Address: [illegible] Heart Disease Research and Training Center, [illegible] Medical Research, 6[illegible] South Wood [illegible], Chicago, Ill. 60612.

A biopsy of the left gastrocnemius muscle showed (1) mild chronic interstitial myositis and (2) encysted trichina in an inactive stage. The two processes were considered to be separate, with the suggestion that collagen disease might be related to the former diagnosis. The skin was not biopsied at this time. No diagnosis was established on this admission, although a diagnosis of scleroderma was considered to be probable. He was given prednisone with some degree of symptomatic relief and was discharged.

He continued to have stiffness of his hands and fingers and pain in his wrists. Episodes of blanching and coldness of the hands and feet occurred. It was noted that, commencing about 1 year after the onset of his illness, the skin over his chest appeared to be shiny and taut.

In April 1957 the patient began to experience dizzy spells and to feel faint while walking, and he had one episode of syncope. Upon his rehospitalization (University Hospital, Baltimore), physical examination showed tightness of the skin over his face, extremities, and abdomen, cold blanched hands and feet, and generalized hyperpigmentation with a few areas of depigmentation over the hands. Laboratory studies revealed a negative serologic test for syphilis, hemoglobin 15.9 Gm. per cent, hematocrit 47.5 per cent, erythrocyte sedimentation rate of 15 mm. per hour, 9,500 leukocytes per cubic millimeter, and 2 per cent eosinophils in a normal differential and smear. Urinalysis was again negative. An electrocardiogram taken on May 25, 1957, showed a regular sinus rhythm with occasional atrial and ventricular premature systoles. P-R was 0.19 second and there was now an intraventricular block with a QRS of 0.14 second. The QRS pattern of right bundle branch block showed a wide deep S in Leads II, aVF, III, and in V5 and V6. It was entirely upright in Lead I and in Lead V1 and V2 with notching and showed a later prominent R in Lead V1. X-ray films of the hand, chest, and esophagus were normal, but the small bowel showed a delayed transit time, segmentation, alternate narrowing and dilatation over an extensive area, which suggested a generalized enteritis. An electroencephalogram was normal. Blood sugar rose only slightly after an oral glucose tolerance test.

In February 1958 the patient was rehospitalized in acute distress with a series of severe syncopal attacks. His pulse was 88 and irregular and the blood pressure was 98/65 mm. Hg. In an observed attack his pulse was noted to be slow or absent and an electrocardiogram showed an irregular idioventricular rhythm with periods of asystole up to 6.6 seconds. Subsequently, atrioventricular conduction returned at times with the P-R interval within normal limits.

After he was discharged on a maintenance regimen of sublingual isoproterenol, oral atropine, and prednisone, edema developed; this was treated by a limitation of salt in the diet and by chlorothiazide. He lost weight and strength and was again hospitalized at the end of April because of severe and frequent syncope. At this time there were medium crepitant basal râles bilaterally, and his heart was slightly enlarged to percussion. His blood pressure was 105/60 mm. Hg. Clinical laboratory studies were normal; tuberculin test was positive. An x-ray film of the chest showed diffuse cardiac enlargement. The electrocardiogram at this time revealed a regular sinus rhythm with partial A-V block and occasional ventricular premature systoles. P-R was 0.22 second, and there were transient periods of 2:1 A-V block. The intraventricular block pattern was unchanged. After a month he was transferred to Levindale for chronic care.

A normal A-V conduction time (P-R = 0.20 second) (Fig. 1, A) was sometimes noted during the ensuing 6 to 7 months; then conduction became consistently prolonged with A-V block which varied from partial to complete (Fig. 1, B) for another 5 months. Long periods of electrocardiographic monitoring were combined with efforts to relate the onset of syncope to alterations in vagal or other reflex influences by producing changes in posture, exertion, position of his head, and by following the consequences of eating, straining at stool, etc. Neither this nor attempts to modify his cardiac arrhythmia by atropine, alkalies, isoproterenol (Fig. 1, C), or striking his chest, nor the use of an external electrical pacemaker provided consistent information. His episodes of syncope were sometimes associated with the development of intermittent complete A-V block and slow idioventricular rhythm, either clinically or electrocardiographically determined. Atrial and ventricular irritability were also present, with multifocal premature beats and with clinical tachycardia. These suggested the possibility that unstable ventricular rhythm might contribute to his episodes of unconsciousness, but none was documented. No record of the effectiveness of the external pacemaker could be obtained, for it was not tolerated by the patient when he was conscious.

Although there was apparent regression of his cutaneous manifestations, the waxy taut appearance remained evident on his face as well as on his chest, hands, and fingers. His heart was now definitely enlarged on physical examination, but sounds remained of good quality without murmurs. Again laboratory studies were eventually normal, including tests of hepatic function, and eosinophilia was no longer present.

In May 1959 complete A-V block became established. From this time on his syncopal episodes were less frequent and he was relatively stable and comfortable at ventricular rates of from 26 to 44 per minute. The QRS of the idioventricular pacemaker was 0.17 second in duration, still with a late R in Lead V1, but predominantly inverted in Lead I with a prominent S in Leads I and V5 to V6. A biopsy of the skin and muscle taken over the left pectoral area in June 1959 at Sinai Hospital, Baltimore, was found by Dr. Tobias Weinberg to be compatible with scleroderma and is described below. Ethylenediamine tetra-acetic acid salt (sodium Versenate*) given intravenously was without any detectable favorable or adverse effect on the electrocardiogram, serum calcium, or phosphorus, or on the clinical manifestations. In August

*Supplied through the courtesy of Dr. ... Riker Laboratories, Inc., Northridge, Calif.

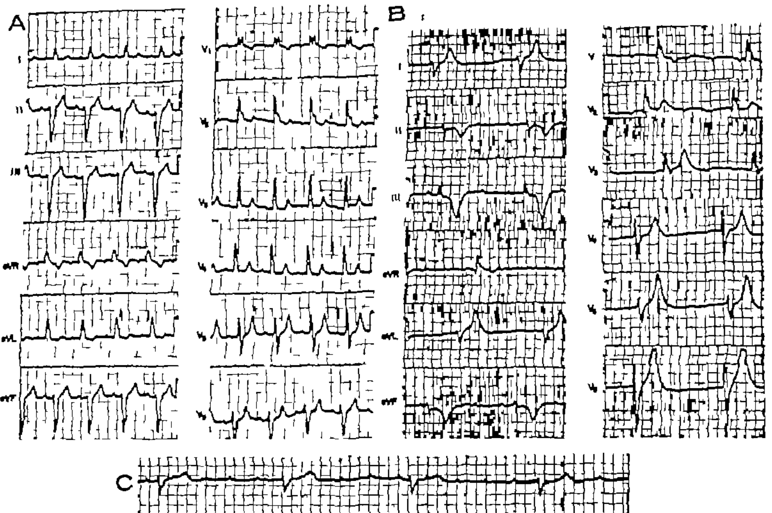



Fig 1 A Electrocardiogram taken Dec 16 1958 shows normal A V conduction with intraventricular block. B Record taken Feb 24 1959 during a period of complete heart block. C Record taken on May 24 1959 7 minutes after sublingual isoproterenol shows complete block uninfluenced by medication

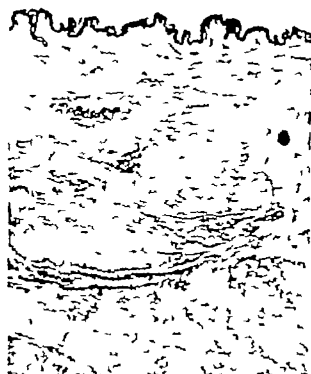


Fig 2 Biopsy of skin Hematoxylin-eosin stain ×47 Note the increase in relatively acellular collagen in the deep corium and subcutaneous fatty tissue

1959 because further cardiac enlargement was noted the venous pressure was 170 mm of water and the circulation time (Decholin) was 30 seconds digitalization was cautiously begun After oral dosage of between 0 5 and 1 0 mg of digoxin bigeminal rhythm was noted with ineffective ventricular premature beats and a pulse rate of 26 A more regular rhythm returned when the drug was stopped Because of this adverse effect the patient was never fully digitalized In October 1959 he was permitted to go home and in a syncopal attack on Nov 17 1959 he was brought to Lutheran Hospital and pronounced dead on arrival An autopsy was performed at this hospital

*Biopsy of the skin and muscle (taken Jan 1959)* There was a marked proliferation and straightening of the collagen fibers in the deep corium and the subcutaneous tissue (Fig 2) Very few fibroblasts were present in this area There was infiltration of mononuclear cells around the vessels and some of the skin appendages The vessels and the epithelium however showed no changes The muscle showed no changes

## Postmortem examination

Aside from the findings in the heart the pathologic diagnoses were (1) Chronic esophagitis with leukoplakia and marked fibrosis of the muscularis (2) Marked fibrosis of the muscularis of the intestine (3) Pulmonary fibrosis and emphysema (4) Marked chronic passive hyperemia (a) of the lungs (b) of the liver with central necrosis (c) of the spleen with fibrosis and (d) of the kidney with cloudy swelling (5) Focal pyelonephritis (6) Pulmonary edema with hemorrhage (7) Acute degeneration of large arterioles in lungs heart kidney and gastrointestinal tract

*The heart*

GROSS EXAMINATION The autopsy was performed 12 hours after death The opened heart was immersed in 4 per cent formaldehyde in toto and sent to one of us (M L )

The heart was enlarged and weighed 451 grams (fixed) The epicardium over the right ventricle and both atria showed large areas of thickening and smaller more discrete plaques were present on the anterior wall of the left ventricle The right atrium was enlarged and its wall was thickened Hemorrhagic zones were present in the right atrial appendage The tricuspid orifice was enlarged

The right ventricle was enlarged and

its muscular wall was thinned in the conus region. Here a considerable layer of fat penetrated from the epicardium almost to the endocardium. The endocardium of this chamber showed focal hypertrophy and the pulmonic valve presented increased hemodynamic changes. The left atrium was questionably enlarged but its wall was thicker than normal. The mitral valve showed nodose thickening at the line of closure and at the edge with some thickening of some of the chordae. The left ventricle was slightly enlarged but its wall was of average thickness. Its endocardium was thickened at the base. The myocardium on section showed fibrotic strands. The right coronary artery was somewhat narrowed.

MICROSCOPIC EXAMINATION

*Methods.* The entire heart including the entire conduction system was studied histologically in a manner previously described.[14] Specifically, the S-A node and its approaches were serially sectioned at 7 μ and every twentieth section was retained. The approaches to the A-V node, the A-V node, the penetrating portion of the bundle and the beginning of the branching portion were serially sectioned at 10 μ and all sections were retained. The remainder of the branching bundle and left and right bundle branches up to the muscle of Lancisi were serially sectioned and every tenth section was retained. The remainder of the right and left bundle branches up to the region of the moderator band was serially sectioned and every twentieth section was retained. The remainder of the septum and walls were cut into blocks and two sections were cut from each block. All of the above mentioned sections were alternately stained with hematoxylin eosin and elastic van Gieson stains. In this manner 4,850 sections were examined. Also several sections were stained for metachromasia by the Hotchkiss method for glycoprotein and by the Congo red method for amyloid.

*Findings*

Left Ventricle—The trabecular area in the subendocardial third of the myocardium was diffusely replaced by a loose tissue containing collagenous and elastic fibers. In these regions there was a dearth of Purkinje fibers and those that were present showed degenerative changes. The subendocardial portion of the myocardium at the base showed marked replacement by hyalinized connective tissue (Fig. 3). The remainder of the myocardium presented a proliferation of fine and coarse elastic and collagenous fibers both perivascularly and between the muscle fibers with scattered areas replaced by vascular and nonvascular



Fig. 3. Section through the base of the septum in the left ventricle showing fibrosis and hyalinization in the subendocardial region. Weigert van Gieson stain ×22

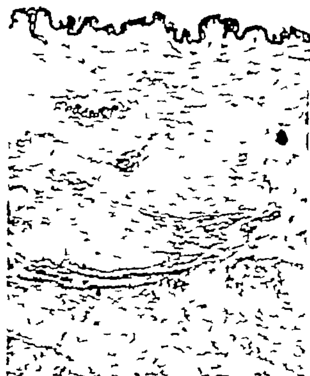


Fig 2 Biopsy of skin Hematoxylin-eosin stain X4 Note the increase in relatively acellular collagen in the deep corium and subcutaneous fatty tissue

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The right ventricle was enlarged and

myocardium and endocardium showed a great infiltration of fat tissue

Atria—There was a marked prolifera tion of the elastic and collagenous tissue perivascularly and between muscle cells of both atria with occasional degeneration of the myocardial cells (Fig 5) and hemorrhage in the right atrium

Conduction System—

S-A node There were no changes

Approaches to the S-A node There was marked proliferation of the elastic and collagenous tissue perivascularly and between muscle cells in the myocardium with occasional acute degeneration of muscle cells hemorrhage and chronic inflammation Some arterioles showed marked thickening of the internal elastic lamella with fragmentation of the elastic tissue of the media and proliferation of collagen of the adventitia Occasionally there was also proliferation of the intima

Approaches to the A-V node Focal proliferation of the elastic and collagenous tissue of the myocardium with degeneration of muscle cells and an infiltration of mononuclear cells was present

A-V node The node was normal in its initial portion However more distally the elastic network around the cell became progressively more accentuated (Fig 6)

A-V bundle penetrating No bursa was present around most of the bundle the latter was more or less fused with the central fibrous body (Fig 7) The cells of the bundle close to the connective tissue of the central fibrous body were greatly swollen vacuolated with pyknotic nuclei (Fig 8) in some cases This process was more severe distally Parts of the bundle



Fig 6



Fig 7

Fig 6 Section through the A-V node showing elastosis of most of the node with the exception of that adjacent to the central fibrous body Weigert Gieson stain X40 Arrows point to the node

Fig 7 Section through the penetrating portion of the A-V bundle showing absence of the sheath in it portion Elastosis present in the lower portion but not the uppermost portion Weigert van Gieson X40 Arrows point to the bundle



Fig. 8. Section through the upper part of the penetrating portion of the A-V bundle showing marked vacuolar degeneration of the bundle cells adjacent to the central fibrous body. Hematoxylin-eosin stain ×154.

showed accentuation of the elastic network, whereas parts adjacent to the central *fibrous body showed a decrease in elastic* tissue (Fig. 7).

A-V bundle branching. This portion was very short and showed changes similar to those seen in the distal portion of the penetrating portion.

Bifurcation. The acute degenerative changes mentioned above were very severe here. This was accompanied by considerable accentuation of the elastic network.

Right bundle branch. The right bundle branch showed marked proliferation of elastic and collagenous fibers which replaced part of the structure with acute degeneration of cells in all three parts (Fig. 9). This was especially marked in the third part.

Left bundle branch. The elastic and collagenous network was proliferated in the beginning with degeneration of Purkinje cells (Fig. 10). More distally there was more marked fibrosis (Fig. 10 *B*). The degeneration of cells was seen throughout the left bundle branch up to the periphery. In some areas there was a dearth of Purkinje cells and an infiltration of lymphoid cells. The terminal Purkinje cells likewise showed marked degeneration.

## Discussion

Pathologic changes in the heart in scleroderma were first *alluded* to by Hektoen. Cardiac involvement in a clinical sense does not occur frequently. The case for *primary* myocardial involvement in systemic scleroderma has been well argued with a convincing although limited clinical demonstration. A number of *secondary* modes of cardiac derangement may complicate and even dominate the picture: pulmonary hypertension, systemic hypertension and hypertensive heart disease, the (probably) rarer involvement of coronary arteries[14] and, at least in the male, the ubiquitous incidental association of coronary atherosclerosis. Lesser degrees of direct myocardial involvement are likely to be recognized in proportion to the frequency of search and the sensitivity of the index used, even though clinical manifestations may be lacking, ascribed to other features of the disease or to other coexisting disorders.

Our case clinically falls into the category of generalized scleroderma with cutaneous, gastrointestinal, and cardiac findings. This is confirmed by the biopsy of the skin and the autopsy findings. The biopsy of the skin revealed an overgrowth of dense




Fig. 9. Sections through the right bundle branch. A, End of first portion showing fibrosis and elastosis with partial replacement of the bundle. Weigert–van Gieson stain ×40. B, Second portion of right bundle branch showing replacement of most of cells by fibroelastic tissue and degeneration of the remaining cell. Hematoxylin-eosin stain ×233. C, Junction of second and third portions of right bundle branch showing fibroelastic replacement of part of bundle with degeneration of the remaining cells. Arrows point to the right bundle branch.




Fig. 10. Sections through the left bundle branch. *A*, Beginning portion showing fibroelastic replacement of parts of the bundle with degeneration of many of the remaining cells. Hematoxylin eosin stain, X137. *B*, Bundle farther down. Weigert van Gieson stain, X41. Arrows point to the left bundle branch.

straight relatively acellular collagenous tissue in the deep corium and the subcutaneous fat tissue. This deep location of the process has been documented by Allen. Autopsy revealed chronic esophagitis with leukoplakia and fibrosis of the smooth muscle of the esophagus and the intestines in addition to the finding in the heart.

The heart showed diffuse fibroelastosis of the myocardium with replacement of most of the subendocardial third of the myocardium of both the left and right ventricles by fibroelastic loose and dense connective tissue. Likewise, such areas were found elsewhere in the myocardium and subepicardially. These areas were mostly unrelated to vascular changes, and the relatively mild narrowing of the right coronary artery would not account for these changes. The lack of hemosiderin may be an added factor in favor of this interpretation.

The findings of an encysted trichina in the muscle biopsy does not warrant the concept of the myocardial findings being the end stage of so-called chronic trichinous myocarditis. In the first place, there was no reaction about the cyst, and healed trichinosis is found in a considerable percentage of the population. Second, it is the considered opinion of most workers[4] that trichinosis produces an acute myocarditis which either is fatal or heals within 6 weeks. Only a few cases have been documented as ending fatally after 10 months. Furthermore, acute trichinous myocarditis responds to steroids, whereas no such reaction was found in this case.

The findings in the conduction system (Fig. 11) may be closely correlated with the electrocardiographic findings. The early intraventricular conduction abnormality may be explained by the progressive fibrotic replacement of the myocardium throughout the ventricles. This was followed by intraventricular block with a right bundle branch block pattern, which is related to the progressive fibroelastic replacement and more recent degenerative changes in the right bundle branch. Although the left bundle branch showed similar changes, because of its wide distribution these changes were not manifested electrocardiographically until later

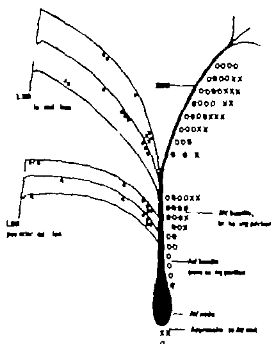


Fig 11 Diagrammatic sketch of the conduction system showing pathologic change X = Old change O = Recent change

when complete A V block occurred The restoration of normal A V conduction time after periods of complete block which continued to occur for over 1½ years after the onset of syncopal attacks is further indication that the A V block was largely produced by progressive destruction of both right and left bundle branches The change in the A V node and bundle of His are of a lesser magnitude than those in the bundle branches The influences of the former changes cannot be excluded since persistent P R prolongation and 2 1 block did occur before complete block was chronically established Some involvement of sympathetic neuroeffector endings is also possible in view of the period of varying A V conduction and of the atrial and ventricular irritability which was noted even before Isuprel was used Involvement of the bundle branches to produce A V block is well known and the extent of the pathologic change is in keeping with other cases in which heart block has been produced [7]

The pathologic process in the bundle of His and bundle branches sheds some light on the assumed basic change occurring in the heart in generalized scleroderma At present it is assumed that there is a marked overgrowth of collagen which results in secondary degenerative changes in the myocardium This is seen best in the A V bundle

The A V bundle normally is surrounded by a sheath or bursa [8] which apparently permits it to lie relatively loose in the central fibrous body This sheath is considerably replaced by connective tissue in our case and apparently correlated with this are the severe acute degenerative changes in the cells of the bundle In the areas close to the central fibrous body the degeneration is most intense whereas it is less so elsewhere in the bundle And it is precisely adjacent to the central fibrous body that the elastosis is least pointing to the probably secondary elastic transformation of connective tissue related to changes in tension

Apart from electrocardiographic manifestations of chamber hypertrophy the frequent occurrence of left bundle branch block right bundle branch block and partial heart block and the occasional occurrence of complete heart block in scleroderma heart are probably best explained as involvement of the bundle branches by the collagenous overgrowth with secondary degeneration although some cases of partial or complete heart block may be due to the changes in the bundle itself

## Summary

A case of generalized scleroderma with maximal involvement of the heart is reported Electrocardiographically there were progressive changes ending in complete A V block Comprehensive studies of the conduction system revealed marked old replacement of both bundle branches by fibroelastic tissue which is considered to be the cause of the block The acute changes in the bundle confirm the prevailing thesis that collagenous proliferation is responsible for the myocardial changes

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# Prolonged depressing effect of premature supraventricular beats

## A mechanism causing transient ventricular standstill

William Dressler, M.D.*
New York, N. Y.

Premature atrial beats which disturb the sinus rhythm are usually followed by a pause which, although noncompensatory, is longer than the initial cycle.[1,2] The prolongation is accounted for by the time required by the premature excitation to reach the sinus node.[3] In addition, it has been shown that on occasions the premature stimulus, by breaking into the pacemaker, exerts a depressing effect.[4] The resulting slowing down of the sinus node, which is manifest through one or several sinus cycles,[4] is not dependent on vagus action, for it has been observed also in the atropinized experimental animal.[5] The depressing mechanism is probably of the same kind as that responsible for the preautomatic pause which, after inhibition of the regular pacemaker or interruption of A-V conduction, precedes activation of the lower center. Edelist and associates[6] have shown in patients with inserted pacemakers in whom either the right atrium or the right ventricle was stimulated electrically that, with an increasing rate of stimulation, there was a progressive lengthening of the escape interval of the patient's own pacemaker. This temporary depression of the formation of impulses became more marked in digitalized patients and was then probably associated with a depression of conduction of impulses.

Premature atrial beats may show a disturbance of A-V conduction, either delay or failure.[3] The disturbance is exaggerated when conduction of the regular beats is impaired. The earlier the premature excitation occurs, the more likely that it finds the junctional tissues in the refractory state. Even blocked premature atrial beats may have a profound influence upon the production of impulses and A-V conduction in the following beats.[3] Langendorf[8] has stressed the role played by concealed conduction in the development of these disturbances. Observations to be reported here seem to indicate that a depressing effect of premature excitations upon A-V conduction may also be a factor.

Premature atrial beats do not commonly exert a depressing action. Such an effect depends on a hypodynamic state of the heart. It has been observed in the experimental animal when experimentation was prolonged or when the vitality of the heart was reduced by the effect of cold, asphyxia, or quinidine.[4] In man likewise inhibiting effects upon the pacemaker seem to occur in the presence of heart disease.

In the following report 4 cases are described which demonstrate a marked and sustained depressing action of pre-

From the Department of Medicine, the Maimonides Hospital of Brooklyn, Brooklyn, N. Y.
Received for publication Oct. 7, 1963.
*Address: 1150 Fifth Ave., New York 28, N. Y.

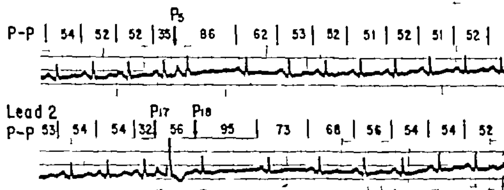



Fig. 1. Case 1. The two strips are continuous. A regular sinus rhythm with a cycle length ranging from 0.51 to 0.54 sec. is interrupted by premature atrial beats (arrows). P5 is followed by a pause which is more than compensatory, and the next sinus cycle is still prolonged. P17 and P18 are both premature. The returning cycle is 0.95 sec. long, that is, more than compensatory, and the following three sinus cycles are still longer than the average sinus period.

mature atrial beats upon the pacemaker and, it is believed, also upon A-V conduction.

**Report of cases**

*Case 1.* N. E., a 68-year-old man, suffered an extensive myocardial infarction 6 months prior to examination.

Fig. 1 shows a regular sinus rhythm with an average rate of 113 per minute. The length of the sinus cycle varies from 0.51 to 0.54 sec. The sinus rhythm is interrupted by premature atrial beats (P5, P17, and P18). The coupling of P5 is 0.35 sec.; the length of the returning cycle measures 0.86 sec. The combined lengths of these periods are longer than two regular cycles. The sinus period which follows the returning cycle is still prolonged, measuring 0.62 sec.

P17 has a coupling of 0.32 sec. Its ventricular complex is aberrant in shape. P18 is probably also premature, since it falls after an interval of 0.56 sec. instead of an expected prolonged pause similar to that following P5. Its ventricular complex is normal in shape because the extrasystole falls later in diastole and the refractory period following P17 is short because of the short length of the preceding cycle. The sinus cycle which follows P18 measures 0.95 sec., that is, it is of more than compensatory length. The next three sinus cycles are also prolonged, measuring 0.73, 0.68, and 0.56 sec., respectively.

COMMENT. In this case premature atrial beats arriving early in diastole are followed by longer than compensatory pauses. This is due to a depressing effect upon the pacemaker which is more intense and protracted when two premature beats occur in sequence. Delay in the production of impulses affects then several sinus periods.

*Case 2.* L. Z., a 64-year-old man, suffered from calcific aortic stenosis and congestive heart failure.

Fig. 2 shows four strips which form a continuous tracing. In the top strip, *A*, a regular atrial tachycardia with inverted P waves and 2:1 A-V block is noticed. The atrial rate is 130 per minute. The cycle length measures 0.46 sec. P13 is a premature atrial contraction which falls after an interval of 0.31 sec. It is followed by an atrial pause which lasts 13 sec. and is interrupted by nodal escaped beats. Upright P waves appear in strip *C* (*arrows*) in intervals which gradually decrease from 2.14 to 1.90 sec. The first of these P waves is blocked; the second and third are apparently conducted, the former with a P-R interval of 0.20 sec. and the latter, which falls earlier in diastole, with a P-R interval of 0.52 sec. In *D* the first P wave is not conducted because of interference with a nodal escape. Then a regular sinus rhythm is established, with a cycle length of 0.91 sec. and a P-R interval of 0.19 sec.

COMMENT. In this case an atrial tachycardia with A-V block is abruptly brought

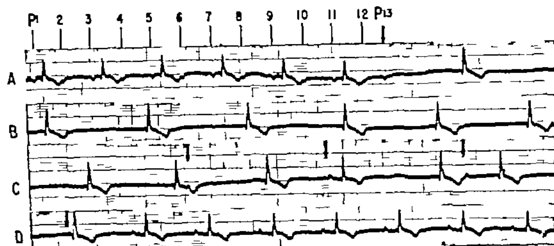



Fig 2 Case 2 Strips A D are continuous Strip A shows a regular atrial tachycardia with 2 1 A V block P13 is premature and appears to bring to a halt the atrial tachycardia An atrial pause of 13 sec ensues which is interrupted by nodal escaped beats In C upright P waves (arrows) appear the second and third of which are conducted In D the first P wave is blocked because of interference with the following nodal escaped beat Then a regular sinus rhythm returns

to a halt after a premature atrial contraction The long atrial standstill that follows is due to the combined depressing effects of the premature atrial beat and the preceding atrial tachycardia

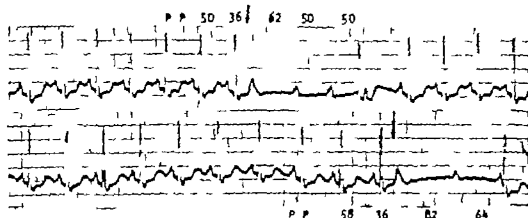
*Case 3* L A a 65 year old woman suffered from Type II A V block with Adams Stokes syndrome which necessitated implantation of a pacemaker Fig 3 *A* was taken prior to implantation It shows two continuous strips of a regular sinus rhythm with an average rate of 111 per minute On two occasions the sinus rhythm is interrupted by a premature atrial beat (*arrows*) which initiates a ventricular standstill

In the upper strip the sinus cycle measures 0 50 sec The premature atrial contraction has a coupling of 0 36 sec Not only is the premature P wave blocked but also the two following sinus excitations although the first sinus cycle is prolonged measuring 0 62 sec and the following sinus periods measure 0 50 sec the same as the initial cycles The first P wave after the ventricular standstill is blocked because it follows closely an escaped beat

In the lower strip of Fig 3 *A* the length of the sinus period has increased to 0 58 sec A premature atrial contraction (*arrow*) arrives after a pause of 0 36 sec and is blocked The returning cycle measures 0 82 sec and the following sinus period 0 64 sec Although these cycles are longer than the initial sinus period affording a longer than average rest period no A V conduction takes place The ventricular standstill is concluded by a nodal escaped beat

In the original electrocardiogram there were more than thirty premature atrial beats each of which initiated a period of ventricular standstill due to A V block

COMMENT In this case of Type II A V block regular sinus rhythm with normal A V conduction is frequently interrupted by a premature atrial beat which is blocked Although the following sinus cycles are prolonged one or two sinus excitations after the premature beat are not conducted to the ventricle This is thought to be due to a depressing action exerted upon A V conduction by the premature atrial excitation which partially penetrates into the junctional fibers Pick and associates have offered a different interpretation in a similar case They thought that A V conduction of the sinus beats was possible only because at a certain length of the sinus period the stimuli fell into the supernormal phase of A V conductivity This condition was disturbed by the occurrence of premature atrial beats so that not only was the premature stimulus blocked but



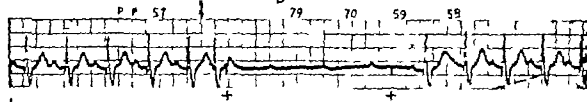




Fig. 3. *A*, Case 3. The two strips are continuous. In the upper strip a regular sinus rhythm with a cycle length of 0.50 sec. is interrupted by a premature atrial beat (arrow) which is fused with the preceding T wave. The returning cycle is 0.62 sec. and the following sinus cycle measures 0.50 sec. Not only is the premature atrial beat blocked but also the two following sinus excitations. The resulting ventricular standstill is concluded by a nodal escaped beat. In the lower strip the initial sinus cycle measures 0.58 sec. Following a premature atrial beat (arrow) the returning cycle is 0.82 sec. and the next sinus period measures 0.64 sec. The premature atrial beat and the following sinus excitation are blocked. The ventricular standstill is concluded by a nodal escaped beat. *B*, Case 4. *A regular sinus rhythm is interrupted by a premature beat (arrow) of either atrial or nodal origin.* The initial cycle measures 0.57 sec. Although the following sinus periods are prolonged, *three P waves* are blocked. Then *normal sinus rhythm* with normal A-V conduction is restored. (Artifacts are marked by +.)

also the *following* normal sinus stimuli. Supernormality was restored by escaped beats which were conducted (concealed) in a retrograde fashion to a region of unidirectional block. This interesting and persuasive interpretation could not be applied to our next case (Fig. 3 *B*) in which A-V *conduction was restored* with out the intervention of an escaped beat.

*Case 4.* M. R., a 50-year-old man, suffered from hypertensive heart disease. Fig. 3 *B* shows a regular sinus rhythm with a cycle length ranging from 0.57 to 0.60 sec. *The P-R interval measures* 0.18 sec. The sixth beat (*arrow*) is premature, arriving after an interval of 0.37 sec. It is of supraventricular type, either atrial or nodal in origin. A premature atrial wave cannot be distinctly made out in the preceding T wave. The premature excitation is conducted to the ventricle and it probably reaches and disturbs the sinus node, for not only is the returning cycle obviously prolonged but also the following two sinus cycles, which measure 0.79 and 0.70 sec., respectively. Hence it is assumed that the *premature atrial excitation depresses the* sinus action. In spite of the increased duration of the sinus cycles, three P waves following the premature beat are blocked. The fourth regular P wave is again normally conducted to the ventricle and *normal sinus rhythm and* A-V conduction are restored.

COMMENT. A regular sinus rhythm with normal A-V conduction is interrupted by a premature beat of supraventricular type. The latter is transmitted to the

sinus node and depresses the production of sinus impulses for three successive periods Although prolonged duration of the sinus cycles affords a longer recovery time for the junctional tissues three P waves following the premature beat are blocked Hence it is assumed that the premature beat depresses not only the regular pacemaker but also A V conductivity

**Summary**

Four cases are reported which demonstrate a sustained depressing effect of premature supraventricular beats upon the pacemaker In one case atrial tachycardia with block is brought to a sudden halt after a premature atrial beat

In two instances premature supraventricular excitations which interrupt a regular sinus rhythm are followed by A V block of one or several sinus excitations Disturbance of A V conduction occurs even though the sinus cycles following the premature beat are conspicuously prolonged allowing the junctional tissues a longer recovery time It is suggested that premature atrial excitations which break into the junctional fibers whether they do or do not reach the ventricle may exert a depressing effect upon A V conduction This is similar in type to inhibition of the pacemaker function with which it is often associated

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# The prognosis of atrial fibrillation after mitral valvotomy

P. B. Halmos, M.D., M.R.C.P.I.*
Belfast, Northern Ireland

It has been estimated that 20 to 50 per cent of patients who undergo mitral valvotomy will develop atrial fibrillation postoperatively.[1-4] The persistence of this arrhythmia is of significance since it has a deleterious effect on the circulation and is associated with a high incidence of systemic embolization.

The present study, based on a review of 1,000 mitral valvotomies, was undertaken to assess the prognosis of postoperative atrial fibrillation and study the effect of various factors on its production and abolition.

## Material

One thousand mitral valvotomies were performed between 1950 and 1964 in Wards 5 and 6 of the Royal Victoria Hospital, Belfast. During the first part of this period, the finger or knife was used to divide the mitral valve, whereas later a transventricular dilator was used. The surgical technique otherwise remained unchanged.

The cardiac rhythm of 855 patients who survived for a week after their first valvotomy was studied. The rhythm was confirmed by electrocardiogram before and usually more than once after operation. All patients were on digitalis preoperatively. None was given prophylactic quinidine. When quinidine conversion was required, it was attempted on the twelfth postoperative day by giving quinidine sulfate in a dose of 3, 6, 9, and 12 grains at 2 hour intervals until conversion was achieved. If required, this regimen was repeated on the second and third days. When sinus rhythm was established, the patient was started on a maintenance dose of quinidine, 3 grains four times a day.

## Results

*Patients in sinus rhythm preoperatively.* Of the 855 patients studied, sinus rhythm was present in 620 (72.5 per cent). One hundred and thirty-seven (22 per cent) developed atrial fibrillation after the mitral valvotomy. It was found that development of atrial fibrillation was more likely in patients over 40 years of age ($p < 0.001$), in those with a history of paroxysmal attacks of severe palpitations ($p < 0.001$), and in those in whom no or only slight division of commissures was achieved at valvotomy ($0.02 < p < 0.05$). Sex, right ventricular hypertrophy, preoperative mitral regurgitation, and the surgeon's estimate of postoperative reflux had no influence on the results.

The onset of atrial fibrillation usually occurred in the first postoperative week and was maximal in the second 24 hours after operation (Fig. 1). The incidence of spontaneous reversion was 13.6 per cent

Received for publication Oct. 11, 1965.
*Royal Victoria Hospital, Grosvenor Rd., Belfast 12, Northern Ireland.

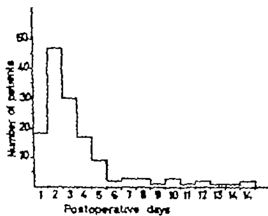



Fig 1 Time of onset of atrial fibrillation after mitral valvotomy

when atrial fibrillation appeared during the first postoperative week and 18 1 per cent when it appeared later Spontaneous reversion to sinus rhythm occurred in a total of 18 patients (13 1 per cent) Quinidine conversion was attempted in the other 119 patients and was successful in 84 (70 5 per cent) The attempt at conversion had to be abandoned because of severe gastrointestinal disturbance in 3 patients Signs of mild toxicity not requiring discontinuation of therapy however were seen in 15 patients Age sex right ventricular hypertrophy and cardiothoracic ratio did not influence spontaneous or quinidine conversion Quinidine conversion was successful in 53 3 per cent of patients who had mitral regurgitation preoperatively and in 75 per cent when the patients showed no evidence of an incompetent mitral valve Sinus rhythm was established in 42 8 per cent of patients in whom only poor division of commissures was achieved The percentage of conversion rose to 74 1 per cent in the group in which mitral obstruction was satisfactorily relieved The above mentioned differences just failed to reach statistical significance at the 0 05 level

*Patients in atrial fibrillation preoperatively* There were 235 patients (27 5 per cent) in this group After mitral valvotomy quinidine conversion was attempted in 15 patients Sinus rhythm was established in 6 (40 per cent) There was one case of spontaneous conversion among the 235 patients Reversion to sinus rhythm occurred in this patient 3 weeks after valvotomy although she has had atrial fibrillation for over 3 years

*Follow up of patients* Of the 18 spontaneous conversions there were 7 reversions to atrial fibrillation after an interval of 1 to 10 years of sinus rhythm The average duration was 4 7 years Sinus rhythm persisted up to the present time in 11 patients with an average duration of 3 6 years (Table I)

Follow up data were available in 80 of the 84 patients in whom sinus rhythm was successfully re established with quinidine Reversion to atrial fibrillation occurred in 60 patients after an interval of 1 month to 9 years The average duration was 2 8 years Twenty of them are still in sinus rhythm In these it has been present for 1

*Table I Follow up results in 18 patients whose postoperative atrial fibrillation converted to sinus rhythm spontaneously (100 per cent follow up)*

| | Sinus rhythm persist | Reversion to atrial fibrillation |
|---|---|---|
| Number of patients | 11 | 7 |
| Longest follow up (yr) | 5 | 10 |
| Average duration of sinus rhythm (yr) | 3 6 | 4 7 |

*Table II Follow up results in 60 patients whose postoperative atrial fibrillation was converted to sinus rhythm with quinidine*

| | Sinus rhythm persist | Reversion to atrial fibrillation |
|---|---|---|
| Number of patients | 20 | 60 |
| Longest follow up (yr) | 7 | 9 |
| Average duration of sinus rhythm (yr) | 3 4 | 2 8 |

*Table III Three year follow up of patients with spontaneous and quinidine conversion*

| | Number of patients | Rhythm | Length of follow up (yr ) 1 | 2 | 3 |
|---|---|---|---|---|---|
| Spontaneous conversion | 15 | SR | 14 | 13 | 12 |
| | | AF | 1 | 2 | 3 |
| Quinidine conversion (postoperative AF ) | 47 | SR | 34 | 25 | 17 |
| | | AF | 13 | 22 | 30 |
| Quinidine conversion (preoperative AF ) | 6 | SR | 1 | 0 | 0 |
| | | AF | 5 | 6 | 6 |

SR Sinus rhythm AF Atrial fibrillation

to 7 years with an average duration of 3 4 years (Table II)

In all 6 patients in whom long standing atrial fibrillation had been abolished post operatively reversion to atrial fibrillation occurred within 1 year within 6 months in 5 of them

When all of the patients who had been followed for at least 3 years were examined the superior prognosis of spontaneous conversion was clearly demonstrated (Table III) In view of the good long term result in the latter group it was compared with the group of patients who maintained sinus rhythm throughout the postoperative period The corresponding figures in these two groups for patients in sinus rhythm at 1 2 and 3 years of follow up were 94 87 80 and 95 93 90 per cent respectively

**Discussion**

The incidence of postoperative atrial fibrillation depends to some extent on preoperative preparation Kittle and Crockett[4] found that although the over all incidence of postoperative atrial fibrillation was 26 per cent in patients who received quinidine and digoxin preoperatively it was only 16 per cent 30 to 35 per cent of their patients who were given either drug or none at all developed atrial fibrillation

The younger the patient the less likely is the development of atrial fibrillation Patients over 40 who undergo valvotomy are particularly susceptible to the development of atrial fibrillation and this is the group in which every attempt should be made to prevent this complication by the use of prophylactic drug therapy A history of previous episodes of severe palpitations is also a good indication for prophylactic therapy

It has been suggested[7] that it is more difficult to establish sinus rhythm in patients who had significant mitral obstruction It seems to be probable that the increased left atrial pressure due to the narrowed valve orifice not only militates against the success of conversion but predisposes to postoperative changes in rhythm This was confirmed by the finding that patients whose significant mitral obstruction was unrelieved at operation were more likely to develop postoperative fibrillation

There have been varying reports of the importance of mitral incompetence in the occurrence of postoperative atrial fibrillation Kittle and Crockett[4] stated that only 1 of their 41 patients who fibrillated after operation had predominant mitral regurgitation Others[3,5,9] found positive correlation between the presence of mitral incompetence and postoperative fibrillation The results in this study did not support the latter findings Postoperative fibrillation was present in 21 7 per cent of patients without and in 27 6 per

cent with mitral insufficiency Severity of reflux as estimated by the surgeon did not bear a positive correlation with the appearance of atrial fibrillation The onset of atrial fibrillation appears most commonly during the first postoperative week. Attention has been drawn to the higher incidence of spontaneous conversion when atrial fibrillation occurred during this period[2,11] Among our patients those developing atrial fibrillation during the second week had a higher rate of spontaneous conversion The small numbers did not allow statistical analysis If conversion to sinus rhythm takes place spontaneously the prognosis is good Eighty per cent of our patients have remained in sinus rhythm for up to 3 years

The over all percentage of spontaneous conversion was smaller in the present series than in most other series reported in the literature A possible reason for this discrepancy is that all patients with recent atrial fibrillation were given quinidine sulfate on the fourteenth postoperative day in an attempt to establish sinus rhythm In the absence of quinidine therapy in some of these patients spontaneous conversion might have occurred at a later date

Quinidine conversion was successful in 72 4 per cent A success rate of 40 per cent was achieved with chronic atrial fibrillation This compares with figures of 70 to 95 per cent reported in postoperative cases[1,2,3] and with 58 5 per cent reported by Eismeyer[11] in 1 058 cases of chronic atrial fibrillation

There were no embolic episodes during conversion It is undoubted that this risk exists but its likelihood has been assessed to be not more than 1 5 per cent in the 48 hours after conversion[1] and is likely to be even smaller in postoperative patients in whom the left atrium has been flushed free of clots and the atrial appendage removed This inherent danger of conversion is more than balanced by the strong evidence for the deleterious effects of continued atrial fibrillation[9,13] and for the circulatory improvement that follows establishment of sinus rhythm[14,15]

The relapse rate among patients requiring quinidine for conversion was disappointingly high Our results indicate that it is not worth while to attempt conversion in patients who fibrillated prior to operation since reversion to atrial fibrillation occurred in 83 per cent of them within 6 months

Patients who require quinidine for postoperative atrial fibrillation will eventually suffer a recurrence of this arrhythmia However 50 per cent of them were in sinus rhythm after 2 years and 30 per cent after 3 years Since it is impossible to predict the prognosis of the individual case conversion in every patient seems to be justified Bloom[16] reported one patient with preoperative atrial fibrillation in whom spontaneous conversion to sinus rhythm occurred after valvotomy He could find no other documented cases in the literature We have encountered one such case out of 235 patients We can only assume that in our case the onset of atrial fibrillation was not caused by severe rheumatic involvement of the myocardium but was initiated and maintained by the high left atrial pressure stretching of the atrial wall and the abnormal hemodynamic situation caused by the tight mitral stenosis Once these factors were relieved sinus rhythm returned


## Summary

The prognosis of atrial fibrillation occurring after mitral valvotomy has been reviewed

Six hundred and twenty patients were in sinus rhythm preoperatively Atrial fibrillation developed in 137 (22 per cent) In 18 (13 1 per cent) of these conversion to sinus rhythm occurred spontaneously quinidine was successfully used with the same end result in 84 (72 4 per cent)

Conversion of long standing atrial fibrillation was successful in only 40 per cent of cases

Once sinus rhythm was established those in whom conversion had occurred spontaneously had the best prognosis


I wish to thank Dr J F Pantridge for his permission to study these patients who were all under his care


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# Exercise escalator

## For electrocardiographic studies in patients with coronary heart disease

*S A Talbot PhD**
*Ivan Likar MB BS*
*W K Harrison Jr PhD*
*Baltimore Md*

The exercise testers now used for cardiac investigation were designed for various purposes. Treadmills were developed especially for studies of cardiorespiratory function in persons in a fair degree of health. Bicycle ergometers similarly were designed in Europe mainly for research in physiology rather than pathology. The various step tests were indeed intended to differentiate between subjects of uncertain cardiac status at milder levels of exercise. However they were hardly designed for use with the recent techniques of multilead electrocardiographic recording throughout exercise for exercise maintained at a controlled level of tachycardia nor for clinical investigations involving the old and infirm. For the latter purposes all three of the usual methods have certain disadvantages.

In this country step tests are the most widely used. For the present purpose the main difficulties are that the rate of exercise is hard to regulate and that many patients are awkward and unstable in stepping up and down rapidly when hampered by the electrodes and cable needed to record 12 leads in exercise electrocardiography. During rapid intermittent exercise these electrodes are frequently jarred loose and artefacts appear in the record particularly in patients who are overweight. Furthermore the work performed during step-tests is difficult to express quantitatively chiefly because the effort expended during descent although considerable cannot be stated in terms of work done.

Pedaling on a bicycle is a type of leg exercise to which most subjects are unused in this country. Thus subjects are apt to experience excessive fatigue of the lower limbs before the desired challenge to the cardiopulmonary system is obtained. In our experience many patients have found the requisite balance and coordination difficult or impossible. Of 90 subjects selected for the electrocardiographic exercise test on the Lanooy bicycle 9 were unable to pedal effectively even after practice. Unaccustomed types of exercise are performed more or less inefficiently. Thus it is difficult to infer accurately the physiologic load from the recorded work in any particular individual.

Ordinary walking is natural and thus appears to be an ideal type of work for most physiologic studies and particularly exercise electrocardiography. This principle is applied in treadmill exercise. The usual motor-driven machine however has serious

This work was supported mainly by Grant GM10095 from the National Institutes of Health
Received for publication Oct 18 1968
*Address The Johns Hopkins Medical School 725 North Wolfe St Baltimore Md 21205

drawbacks when used for exercising patients suspected of having coronary heart disease. During the test there is real danger of falling, and in an emergency it is not possible to stop the motion rapidly, so that an additional technician is required as a "catcher." Apprehension induced in some people by the treadmill exercise adds to the patient's discomfort and produces psychological stress that is significantly disturbing in cardiac tests.

In the attempt to overcome these disadvantages, we have designed an exercise tester that is especially suited for multilead electrocardiography during the exercise of patients with coronary heart disease. For this we have used the treadmill principle for an "escalator" to be driven entirely by the patient's own weight and under his control (Fig. 1). Such a device has the following advantages: (1) It presents minimal danger to the weak and unsteady, for it automatically arrests as soon as walking stops. (2) It mainly exercises the muscles habitually used by nonathletic people. (3) The pattern of muscular co-ordination is already well learned, so that the effect of training is minimized. The relative immobility of the upper part of the body during steady exercise permits excellent quality multiple lead in exercise electrocardiograms. (4) The rate of work (power) is directly proportional to the speed of stepping. This speed can be regulated by the physician either for constant stepping rate (power) or with cardiotachometer for constant heart rate (effort). Adjustment is made by means of a manual valve controlling a hydraulic load. (5) The mechanics of such a device are simple, calibration does not change, and there is no external power requirement. Unlike bicycle ergometers, no minimum speed



Fig. 1. Exercise escalator showing position of patient during exercise. Dials for weight, speed, and work rate are at right.

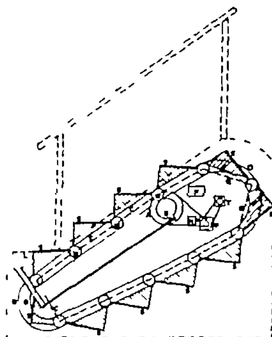


Fig. 2. Schematic diagram of exercise escalator. Eleven steps (*S*) hinge to each other at wheels (*W*) which are constrained to move in a groove between a pair of oval tracks (*O*). Attached roller chains (*C*) drive sprockets (*A*), the shaft of which is connected by belts to an oil pump (*P*). This pump then circulates oil through a manual needle valve (*N*) which controls the speed. The tachometer (*T*) indicates this on a voltmeter (*V*). A hinged landing (*L*) actuates a brake (*B*) when the patient descends to this level. Banisters guard the patient, and suitable enclosures reduce the perception of height.

need be imposed Maintenance does not require a specialist

**Design of the exercise escalator**

The design of the exercise escalator appears schematically in Fig 2 This figure shows 11 light wooden 7 inch steps coupled together These steps rest on a set of ball bearing wheels each rolling in a groove between a pair of oval tracks As the steps move down under the patient's weight roller chains on either side drive a sprocket the shaft of which is connected by a belt to a hydraulic gear type of pump This pump circulates oil through a constrictor valve which provides the main workload and controls the speed Speed of walking is sensed by a tachometer which generates a voltage scaled in watts kilogram meters per minute or steps per minute as desired A scaling factor which is the patient's weight is preset by a direct reading potentiometer knob Two ranges are provided on the meter 0 to 150 and 0 to 300 watts (900 to 1 800 kg M /min )

A number of engineering problems were encountered minimizing the number of wheels and tracks optimal design of tracks for minimal friction and momentum discontinuity and lightening the moving mass We were especially anxious to provide an automatic subject actuated stopping device This was effected by a set of steel fingers which form the lower landing and actuate a safety brake

The physical principle is simple The work is measured simply by counting steps of known height per minute and multiplying by the subject's weight This work done mainly against gravity is dissipated into various frictional sinks including the needle valve

We have used the escalator for nearly maximal exercise in 32 normal subjects and to provide controlled cardiac loads in 14 patients with coronary heart disease All of the subjects were accustomed to climbing steps and no mishaps occurred The multiple lead electrocardiograms recorded at frequent intervals during the period of exercise were remarkably free of muscle noise and base line drift In contrast during the two-step test numerous artefacts on our multiple lead electrocardiograms were produced by excessive body motion and awkwardness in some of these subjects especially when exercising to a high level of tachycardia

The escalator has certain disadvantages It is bulky with a landing 20 inches above the floor because one must allow for the return path of the steps A more compact design would be more complex Although basically simple the escalator involves considerable machining and assembly of high quality components so that it is no cheaper to build than a good bicycle ergometer

We wish to express our gratitude to Mr A Fabula Chief Engineer of the Escalator Division of Otis Corporation who contributed to the design principles Mr John Kummell was responsible for much of the detailed design drawings and solution of problems of assembly

# Experimental and laboratory reports

## Hemodynamic effects of two beta-adrenergic blocking drugs in anesthetized intact dogs

*John F. Murray, M.D.**
*Edgardo Escobar, M.D.***
*Norman L. Jones, M.D.****
*Elliot Rapaport, M.D.*****
*San Francisco, Calif.*

Drugs which block beta receptors of the sympathetic nervous system are assuming importance as potential therapeutic agents and as tools for physiologic investigation. Koch-Weser[1] recently emphasized that ideally drugs used to block beta receptors should do so without significantly stimulating or depressing the heart by direct action. The first beta-blocking drug available (3,4-dichloroisoproterenol) abolished the cardiac effects of sympathetic nerve stimulation but exerted sympathomimetic effects of its own. Our purpose was to study in anesthetized dogs the hemodynamic responses that follow the administration of two new beta receptor blocking drugs that are purported to be more specific in their actions. The results show that Nethalide (1-(2-naphthyl)-1)-2-isopropylaminoethanol hydrochloride) produces important changes in addition to its adrenergic blocking effects and that propranolol (1-isopropylamino-3-(1-naphthloxy)-2-propanol hydrochloride) causes responses which are consistent with the concept of beta blockade but through an unknown mechanism of action.

### Methods

Studies were performed on 14 mongrel dogs that weighed between 13.2 and 20.5 kilograms and were anesthetized with intravenous chloralose and urethane (70 and 350 mg. per kilogram, respectively). A cannula was placed in the brachial artery for sampling blood and was connected to a strain gauge (Statham P 23GG) to record pressure. Intrapleural pressure was measured by a mushroom catheter inserted into the right pleural space through a stab wound and connected to a Statham differential manometer (PM131TC). The animals were ventilated with a Harvard respirator through a cuffed endotracheal tube at a minute ventilation sufficient to maintain arterial carbon dioxide tension ($Pa_{CO_2}$) within 8 mm. Hg of initial values

From the Cardiovascular Research Institute, University of California San Francisco Medical Center, San Francisco, Calif.
Supported by United States Public Health Service Grants [illegible], HE 04285 [illegible], and FR-00122.
Received for publication Oct. 4, 196[illegible].
*Associate Professor of Medicine and Physiology, University of California [illegible] Los Angeles; [illegible] Cardiovascular Research Institute, University of California San Francisco Medical Center, San Francisco, Calif. Address: Department of Medicine, University of California School of Medicine, Los Angeles, Calif. 90024.
**International Postdoctoral Fellow of the United States Public Health Service. Present address: Department of Pathophysiology, School of Medicine, University of Chile, Santiago, Chile.
***International Postdoctoral Fellow of the United States Public Health Service. Present address: Department of Medicine, Postgraduate Medical School of London, London W. 12, England.
****Associate Professor of Medicine, University of California San Francisco Medical Center, San Francisco, Calif.

At intervals throughout the experiment the dog's lungs were inflated to a pressure of approximately 30 mm Hg in order to prevent atelectasis

Under fluoroscopic guidance a No 4F catheter with a rapidly responding bead thermistor at its tip* was placed immediately proximal to the aortic valve by retrograde catheterization from a femoral artery to record aortic blood temperature Similarly a No 7F or 8F catheter with a closed end and multiple side holes was positioned in the left ventricle this catheter was used to inject 3 or 4 ml of cooled normal saline rapidly into the left ventricle or to measure left ventricular pressure when connected to a Statham P23gb strain gauge zero level was 6 cm above the base of the animal board Heart rate was monitored with an electrocardiogram Cardiac output was measured by the indicator dilution technique with indocyanine green The left ventricular catheter was preloaded with dye which was rapidly injected while arterial blood was aspirated through a Colson densitometer by a Harvard constant speed withdrawal pump Standard solutions of dye for calibration were made in the animal's own blood at the end of the experiment Pressure measurements indicator dilution and thermodilution records were obtained with an Electronics for Medicine PR 7 recorder

A 15 minute adjustment interval was allowed after the preliminary procedures were completed The control and experimental periods each lasted about 10 minutes during this time we measured cardiac output obtained 8 to 12 aortic thermodilution recordings made a second measurement of cardiac output and midway in the period recorded left ventricular end diastolic pressure intrapleural pressure and brachial arterial pressure Arterial blood was collected to measure $Pa_{CO_2}$ $P_{O_2}$ pH and hematocrit ratio Left ventricular end diastolic transmural pressure was calculated by subtracting mean intrapleural pressure from left ventricular end diastolic pressure measurements were obtained simultaneously during a complete respiratory cycle

Mean values are reported for two cardiac output determinations and multiple thermodilution and heart rate recordings The paired measurements of cardiac output made during control periods differed from mean values by ± 5 9 per cent Left ventricular stroke volume (SV) was computed from the mean cardiac output and heart rate (HR) determinations obtained during each experimental period End diastolic volume (EDV) and end systolic volume (ESV) were derived from the formulas

$$\text{EDV (ml)} = \frac{\text{SV}}{1 - \text{K}} \qquad (1)$$

$$\text{ESV (ml)} = \text{EDV} - \text{SV} \qquad (2)$$

where K = the average ratio of change in temperature of a beat to that of the preceding beat obtained from successive steps of the aortic thermodilution curve Details of the thermodilution technique have been published[8]

Systemic vascular resistance in arbitrary units was calculated by dividing mean arterial pressure (millimeters of mercury) by cardiac output (liters per minute per kilogram) Stroke work index (grams centimeter per kilogram) was calculated by multiplying mean brachial arterial pressure (centimeters of water) minus left ventricular end diastolic pressure (centimeters of water) times SV (milliliters per kilogram)

Mean circumferential shortening rate (MCSR) can be defined as the average velocity of fiber shortening along the inner circumference of the ventricular chamber assuming a spherical ventricle at end systole and end diastole[9]

$$\text{MCSR (cm/sec)} = \frac{2\pi(\text{ed} - \text{es})}{\text{sep}} \qquad (3)$$

where ed = end diastolic radius in centimeters es = end systolic radius in centimeters and sep = systolic ejection period in seconds obtained from the brachial arterial pressure recording

End systolic force was calculated as proposed by Holt[4] from end-systolic circumference and tension derived at end systole* by the Laplace equation

*[illegible] Engineering Corp Springfield N J

[illegible]

$$\text{Tension (Gm/cm)} = \text{LVESP (Gm/cm}^2) \times \text{es (cm)}/2 \quad (4)$$

$$\text{Force (Gm)} = \text{Tension (Gm/cm)} \times 2\pi\,\text{es (cm)} \quad (5)$$

End systolic force and/or MCSR could not be derived once after propranolol (Dog 14, 5 minutes) and twice after Nethalide (Dog 3, 5 and 20 minutes) because damping of the arterial pressure record precluded accurate measurement of LVESP and esp.

After control measurements were performed, 7 of the animals were given Nethalide and 7 were given propranolol. Nethalide, 5.0 mg. per kilogram diluted to 150 ml. in dextrose and water, was administered intravenously over a 15 minute period. Propranolol, 0.5 mg. per kilogram, diluted to 30 ml. in saline, was infused in 5 minutes. All hemodynamic measurements were repeated at the completion of the infusion of the drugs and 15 minutes later. Since the determinations took 10 minutes to perform, these are called the 5 minute and the 20 minute postdrug periods. Subsequently, to test the adequacy of beta adrenergic blockade, brachial arterial pressure and HR were recorded after the intravenous injection of 10 $\mu$g of isoproterenol in 2 minutes; the injection was continued and a single cardiac output (3 to 4 thermal curves) and pressures were recorded rapidly after a total of 20 $\mu$g had been given. In most dogs all observations were then repeated 10 minutes after the intravenous administration of 5 mg. of atropine (total). The extent of neurogenic blockade was further evaluated by the responses of brachial arterial pressure and HR to bilateral carotid arterial occlusion during the control period, after the 20 minute postdrug period, and after atropine was injected.

Statistical techniques were used to evaluate two aspects of the study: (1) the effect of each drug, examined separately, on the variables under consideration, and (2) a quantitative comparison of the two drugs. The first of these was analyzed by using each animal as its own control, and the null hypothesis was that the mean difference between control and drug periods was zero. To compare the effects of one drug with the other, the difference in each variable between control and drug periods in a given animal was treated as the raw datum, and a comparison was made between mean data for the two drugs; the null hypothesis was that there was no difference between the means.[4]

## Results

Data from the 14 experiments are shown in Table I (for Nethalide) and Table II (for propranolol). Dogs No. 7 and 14 were not included in the statistical analysis presented in Table III but are discussed separately because of the difficulty encountered in anesthetizing these animals, which affected control values. The mean values of all hemodynamic parameters measured or derived did not differ statistically between the two groups during the control periods.

*Hemodynamic effects.* Mean cardiac output rose nearly 60 per cent above control values in dogs that received Nethalide ($p < 0.001$) and did not change significantly in those given propranolol. The rise in cardiac output in dogs receiving Nethalide was the result of an increase in both HR and SV. Although there was a tendency for the values to return toward control values 20 minutes after beta blocking drugs were given, the magnitude of the changes in cardiac output and HR responses was still significantly different between drugs.

The ESV/EDV ratio decreased in dogs given Nethalide and increased in those that received propranolol. The changes are significant at 5 and 20 minutes in the animals receiving propranolol and at 5 minutes in the dogs given Nethalide; differences between the two drugs are significant during both the 5 minute and 20 minute postdrug periods. Neither drug caused significant changes in heart size, but since they had opposite influences on ESV and EDV, there are significant differences between the two drugs when compared at 5 minutes (ESV) and 20 minutes (ESV and EDV).

Left ventricular transmural pressure rose above control values 5 minutes after propranolol was given but was not affected

*Table I. Hemodynamic data after the administration of Nethalide (5 mg/kg I.V. in 15 min.)*

| Dog No. | Q (ml/min/kg) | HR (beats/min) | SV (ml/kg) | ESV/EDV (%) | EDV (ml/kg) | ESV (ml/kg) | AP (mm Hg) | LVEDP (mm Hg) | SVR (units)† | SWI (Gm M/kg) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 C | 168 | 84 | 1.99 | 66.6 | 5.96 | 3.97 | 114 | 9.0 | 680 | 2.84 |
| 5 | 293 | 129 | 2.28 | 67.1 | 6.94 | 4.66 | 87 | 8.1 | 278 | 2.29 |
| 20 | 197 | 111 | 1.78 | 66.7 | 5.35 | 3.57 | 93 | 9.6 | 472 | 2.02 |
| 2 C | 152 | 81 | 1.88 | 76.8 | 8.08 | 6.21 | 133 | 12.4 | 877 | 3.08 |
| 5 | 257 | 115 | 2.23 | 68.8 | 7.16 | 4.97 | 147 | 11.1 | 512 | 4.12 |
| 20 | 203 | 98 | 2.07 | 70.9 | 7.12 | 5.05 | 154 | 9.9 | 759 | 4.06 |
| 3 C | 205 | 129 | 2.13 | 60.2 | 5.34 | 3.21 | 152 | 11.2 | 743 | 4.09 |
| 5 | 297 | 127 | 2.29 | 55.9 | 5.19 | 2.90 | 125 | 16.6 | 436 | 3.38 |
| 20 | 231 | 128 | 1.98 | 38.6 | 4.81 | 2.87 | 142 | 9.5 | 558 | 3.57 |
| 4 C | 283 | 114 | 2.47 | 52.0 | 5.14 | 2.67 | 142 | 10.6 | 502 | 4.41 |
| 5 | 455 | 165 | 2.74 | 48.7 | 5.33 | 2.59 | 151 | 8.7 | 332 | 5.30 |
| 20 | 395 | 148 | 2.67 | 53.6 | 5.74 | 3.08 | 161 | 6.5 | 256 | 5.61 |
| 3 C | 157 | 121 | 1.90 | 70.7 | 4.44 | 3.14 | 127 | 20.4 | 808 | 1.89 |
| 5 | 224 | 158 | 1.42 | 63.2 | 3.84 | 2.43 | 96 | 13.9 | 429 | 1.39 |
| 20 | 220 | 160 | 1.38 | 65.9 | 4.04 | 2.66 | 117 | 10.7 | 532 | 2.00 |
| 6 C | 178 | 104 | 1.71 | 74.1 | 6.61 | 4.89 | 131 | 12.0 | 737 | 2.77 |
| 5 | 274 | 140 | 1.96 | 67.9 | 6.11 | 4.14 | 124 | 19.0 | 452 | 2.90 |
| 20 | 195 | 141 | 1.38 | 71.5 | 4.85 | 3.47 | 133 | 9.4 | 681 | 2.32 |
| 7 C | 431 | 229 | 1.89 | 61.5 | 4.93 | 3.04 | 158 | 14.7 | 361 | 3.68 |
| 5 | 312 | 169 | 1.84 | 57.1 | 4.29 | 2.43 | 134 | 15.3 | 495 | 3.47 |
| 20 | 282 | 171 | 1.65 | 58.1 | 3.93 | 2.29 | 155 | 13.0 | 549 | 3.19 |
| Mean | (Dogs 1-6) | | | | | | | | | |
| C | 190 | 106 | 1.91 | 66.7 | 5.93 | 4.01 | 133 | 12.6 | 724 | 3.18 |
| 5 | 299 | 139 | 2.15 | 61.9 | 5.76 | 3.61 | 121 | 12.9 | 415 | 3.25 |
| 20 | 244 | 131 | 1.87 | 64.5 | 5.32 | 3.44 | 133 | 9.3 | 568 | 3.26 |

C, Control period; 5 [illegible] and 20 [illegible] after administration of the drug.
†Systemic vascular resistance [illegible] AP (mm Hg)/Q (L/min/kg)
Q, Cardiac output; HR, Heart rate; SV, Stroke volume; ESV/EDV [illegible] LVEDP, Left ventricular end-diastolic pressure; AP, Mean arterial pressure; ESV [illegible] SVR, Systemic vascular resistance; SWI, Stroke work index.

*Table II. Hemodynamic data after the administration of propranolol (0   mg./Kg. I.V. in 5 min.)*

| Dog No. | Q (ml./min./Kg.) | HR (beats/min.) | SV (ml./Kg.) | ESV/EDV (%) | EDV (ml./Kg.) | ESV (ml./Kg.) | AP (mm. Hg) | LVEDP (mm. Hg) | SVR (units) | SWI (Gm.-M./Kg.) |
|---|---|---|---|---|---|---|---|---|---|---|
| 8 C | 161 | 90 | 1.82 | 54.6 | 4.00 | 2.18 | 154 | 13.4 | 942 | 3.48 |
| 5 | 169 | 103 | 1.63 | 59.8 | 4.07 | 2.43 | 174 | 17.9 | 1033 | 3.46 |
| 20 | 165 | 96 | 1.72 | 59.4 | 4.23 | 2.51 | 162 | 14.6 | 965 | 3.45 |
| 9 C | 217 | 100 | 2.17 | 58.2 | 5.18 | 3.02 | 143 | 15.4 | 653 | 3.76 |
| 5 | 205 | 121 | 1.69 | 64.8 | 4.81 | 3.12 | 145 | 16.4 | 708 | 2.94 |
| 20 | 201 | 108 | 1.58 | 61.3 | 4.57 | 2.98 | 139 | 18.3 | 693 | 3.09 |
| 10 C | 261 | 120 | 2.17 | 65.4 | 6.28 | 4.11 | 171 | 17.7 | 656 | 4.52 |
| 5 | 204 | 135 | 1.51 | 75.9 | 6.25 | 4.74 | 171 | 25.4 | 839 | 2.99 |
| 20 | 202 | 136 | 1.49 | 76.3 | 6.27 | 4.78 | 174 | 19.0 | 860 | 3.14 |
| 11 C | 158 | 108 | 1.46 | 64.4 | 4.11 | 2.65 | 149 | 11.0 | 944 | 2.74 |
| 5 | 152 | 115 | 1.29 | 69.3 | 4.20 | 2.91 | 151 | 13.6 | 993 | 2.41 |
| 20 | 158 | 120 | 1.32 | 65.6 | 4.10 | 2.68 | 151 | 12.6 | 954 | 2.48 |
| 12 C | 207 | 135 | 1.50 | 73.8 | 5.72 | 4.21 | 132 | 16.1 | 648 | 2.56 |
| 5 | 217 | 118 | 1.84 | 75.9 | 7.64 | 5.80 | 136 | 19.9 | 626 | 2.91 |
| 20 | 225 | 117 | 1.92 | 75.4 | 7.79 | 5.87 | 140 | 17.9 | 623 | 3.19 |
| 13 C | 183 | 123 | 1.48 | 58.6 | 3.56 | 2.09 | 131 | 13.1 | 721 | 2.37 |
| 5 | 167 | 106 | 1.57 | 56.9 | 3.64 | 2.07 | 138 | 4.1 | 829 | 2.43 |
| 20 | 175 | 109 | 1.61 | 69.0 | 5.19 | 3.58 | 144 | 22.7 | 821 | 2.66 |
| 14 C | 301 | 149 | 2.03 | 52.9 | 4.29 | 2.27 | 186 | 22.9 | 619 | 4.50 |
| 5 | 255 | 145 | 1.72 | 58.4 | 4.15 | 2.42 | 177 | 55.2 | 693 | 85 |
| 20 | 255 | 138 | 1.85 | 64.4 | 5.18 | 3.34 | 178 | 34.1 | 698 | 3.62 |
| Mean | (Dogs 8-13) | | | | | | | | | |
| C | 197 | 113 | 1.77 | 62.5 | 4.91 | 3.01 | 147 | 14.5 | 61 | 3.21 |
| 5 | 185 | 117 | 1.59 | 67.1 | 5.10 | 3.53 | 153 | 19.6 | 819 | 2.56 |
| 20 | 158 | 114 | 1.66 | 68.3 | 5.43 | 3.77 | 152 | 17.3 | 821 | 3.00 |

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*Table III Statistical comparisons of results in 12 animals receiving either Nethalide (N) or propranolol (P)**

| | Drug + 5 min | | | Drug + 20 min | | |
|---|---|---|---|---|---|---|
| | Δ (C–5 min) | S E M | p | Δ (C–20 min) | S E M | p |
| Q (ml/min/kg) | | | | | | |
| N | 109 | 15.1 | <0.001 | 54 | 13.4 | <0.025 |
| P | −12 | 10.0 | >0.20 | −9 | 10.9 | >0.40 |
| Δ (N − P) | 121 | 18.1 | <0.001 | 63 | 17.3 | <0.005 |
| HR (beats/min) | | | | | | |
| N | 34 | 7.6 | <0.01 | 26 | 6.2 | <0.01 |
| P | 4 | 6.9 | >0.50 | 2 | 5.8 | >0.50 |
| Δ (N − P) | 30 | 10.2 | <0.025 | 24 | 8.5 | <0.025 |
| SV (ml/kg) | | | | | | |
| N | 0.24 | 0.03 | <0.001 | −0.04 | 0.09 | >0.50 |
| P | −0.18 | 0.15 | >0.20 | −0.11 | 0.15 | >0.50 |
| Δ (N − P) | 0.42 | 0.15 | <0.025 | 0.07 | 0.18 | >0.50 |
| ESV/EDV (%) | | | | | | |
| N | −4.8 | 1.3 | <0.025 | −2.2 | 1.2 | >0.10 |
| P | 4.6 | 1.7 | <0.05 | 5.8 | 1.6 | <0.005 |
| Δ (N − P) | −9.4 | 2.1 | <0.005 | −8.0 | 2.0 | <0.005 |
| LVTMP | | | | | | |
| N | 0.3 | 2.0 | >0.20 | −3.3 | 1.4 | >0.05 |
| P | 5.1 | 1.5 | <0.025 | 3.1 | 1.3 | >0.05 |
| Δ (N − P) | −4.8 | 2.5 | >0.05 | −6.4 | 1.9 | <0.01 |
| AP (mm Hg) | | | | | | |
| N | −12 | 8.4 | >0.20 | 0 | 6.9 | >0.50 |
| P | 6 | 3.0 | >0.10 | 5 | 7.4 | >0.05 |
| Δ (N − P) | −18 | 8.9 | >0.05 | −5 | 7.3 | >0.50 |
| SVR† (units) | | | | | | |
| N | −309 | 33 | <0.001 | −156 | 33 | <0.01 |
| P | 77 | 28 | <0.05 | 59 | 33 | >0.10 |
| Δ (N − P) | −386 | 44 | <0.001 | −215 | 47 | <0.005 |

*Doses N [illegible] and 14 mg/kg [illegible]
†SVR (units) = mean AP (mm Hg)/Q (L/min/kg)
F [illegible] to Table I
‡Δ (N − P) Probability value of comparison between N and P. The 5-min and 20-min results are compared with control data (C)

by the administration of Nethalide All the changes encountered were due to variations in left ventricular end-diastolic pressure intrapleural pressure remained constant Significant differences between drugs were apparent in left ventricular transmural pressure at 20 minutes Although the drugs had variable effects on brachial arterial pressure Nethalide caused a significant decrease and propranolol an increase in systemic vascular resistance No significant change occurred in stroke work index

*End systolic force and end systolic circumference* A significant correlation between end systolic force and end systolic circumference ($r = 0.83$, $p < 0.01$) was found for the control data (Fig 1) Twelve

[illegible]

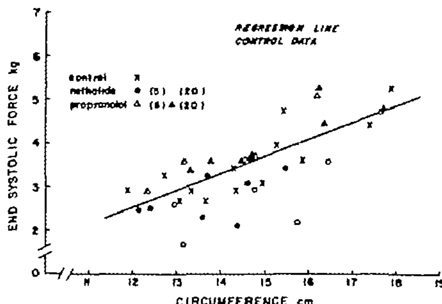



Fig 1 Relationship between end systolic force and end systolic circumference during control periods and after the administration of Nethalide and propranolol

of the thirteen values for end systolic force and end systolic circumference obtained under the influence of propranolol lie above the regression line for the control periods ($p < 0.001$ by sign test) all but one of the twelve results from the Nethalide experiments are below the control regression line ($p < 0.001$ by sign test) Comparison between force values after administration of both drugs and control measurements reveals that Nethalide caused a decrease ($p < 0.001$) and propranolol an increase ($p < 0.01$) in end systolic force

*Mean circumferential shortening rate and end diastolic volume* There is a significant inverse relationship between mean circumferential shortening rate and EDV ($r = -0.55$ $p < 0.05$) during the control periods (Fig 2) After infusion of Nethalide more points are above than below the regression line for the control data but the scatter is very wide All of the values from the propranolol experiments however are below the control regression line ($p < 0.001$ by sign test) Comparison between shortening velocity values after administration of both drugs and control measurements reveals that Nethalide did not change ($p > 0.20$) and that propranolol decreased mean circumferential shortening rate ($p < 0.001$)

*Mean circumferential shortening rate and end systolic force* The relationship between mean circumferential shortening rate and end systolic force during control periods approaches significance ($0.05 < p < 0.10$) (Fig 3) After the administration of Nethalide data are equally above and below the control regression line however all but two of the values from the propranolol experiments lie below the line ($p < 0.01$)

*Responses to isoproterenol* The infusion of 10 µg of isoproterenol produced virtually no change in HR systolic diastolic and mean brachial arterial pressures or systolic ejection period Although isoproterenol was not given to these dogs before the administration of blocking drugs 10 µg causes tachycardia widens pulse pressure and increases contraction velocity in normal animals[8] Twenty micrograms of isoproterenol produced significant changes in ESV/EDV and systemic vascular resistance (Nethalide group) and cardiac output and stroke volume (propranolol group) these indicate that partial breakthrough of the blockade had occurred at the time isoproterenol was given although inhibition was probably more complete at an earlier time

*Responses to atropine* After the effects of

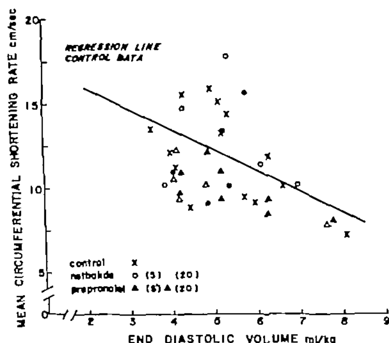



Fig. 2 Relationship between mean circumferential shortening rate (MCSR) and end-diastolic volume (EDV) during control periods and after the administration of Nethalide and propranolol

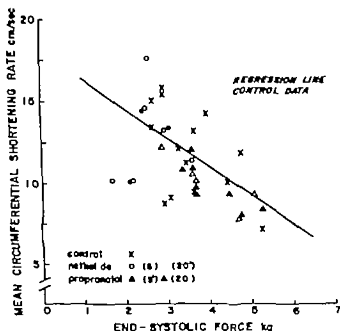



Fig. 3 Relationship between mean circumferential shortening rate (MCSR) and end systolic force during control periods and after the administration of Nethalide and propranolol

isoproterenol were dissipated atropine was given in order to study the effects of combined beta adrenergic and cholinergic blockade The only significant change that followed atropine in dogs which had received Nethalide was a fall in left ventricular end-systolic pressure In dogs that received propranolol atropine had a more noticeable effect causing significant changes in ESV EDV and systemic vascular resistance

*Carotid occlusion* The mean responses to bilateral carotid occlusion during control periods were increases in HR of 31 beats per minute and in arterial pressure of 53 mm Hg These responses were significantly reduced after both Nethalide and propranolol—a rise of 7 beats per minute and 26 mm Hg and a rise of 16 beats per minute and 36 mm Hg respectively

*Duration of action* With few exceptions the hemodynamic changes that followed infusion of both drugs were maximal 5 minutes after administration When the 5 minute and 20 minute intervals are compared in the Nethalide experiments significantly different results were obtained during the later period always toward control values in cardiac output SV ESV EDV ratio mean brachial arterial pressure and systemic vascular resistance No significant difference in any parameter was found between the 5 minute and 20 minute periods after propranolol

*Dogs 7 and 14* One dog that received Nethalide (Dog No 7) and one that was given propranolol (Dog No 14) were not included in the statistical analysis presented in Table III Dog No 7 was difficult to anesthetize and had an extremely high cardiac output that diminished during the course of the experiment (Table I) It is uncertain whether the decline represents a drug effect or spontaneous withdrawal of stimuli occasioned by the traumatic anesthesia Since the changes in cardiac output HR and SV were in general opposite to those in the other animals that received Nethalide the elimination of Dog No 7 from consideration influences the statistical results Dog No 14 also had an elevated initial cardiac output and excessively high brachial arterial and left ventricular end diastolic pressures (Table II) when this dog was given propranolol brachial arterial pressure and cardiac output fell slightly but remained well above usual control values and left ventricular transmural pressure rose to 55 mm Hg Since the changes in Dog No 14 were qualitatively similar to those in the remainder of the dogs that received propranolol its exclusion does not greatly affect the statistical analysis of that group

*Other studies* No changes occurred in Pa Pac pH or arterial hematocrit that could be attributed to the effects of either drug On a few occasions premature ventricular contractions appeared during the administration of Nethalide these could be increased in frequency or made to disappear by changing the rate of infusion In 4 dogs an erythematous flush became apparent in shaved areas while Nethalide was being given and persisted for the remainder of the experiment The flush had the appearance of extreme vasodilatation and was coincident with hemodynamic evidence of high cardiac output and a decrease in brachial arterial pressure and systemic vascular resistance

## Discussion

Nethalide was described by Black and Stephenson[7] as an effective antagonist of beta adrenergic receptors and relative free from intrinsic sympathomimetic activity Recently the results of several investigations show that Nethalide produces a variety of pharmacologic effects in addition to its beta receptor inhibition[8-10] Our data demonstrate that in addition to its beta blocking action Nethalide affects both the heart and peripheral blood vessels

Cardiac output increased above control levels after the administration of Nethalide because of a rise in both SV and HR Donald Kvale and Shepherd[8] also noted an increase in cardiac output and SV after Nethalide (6 mg per kilogram) but the HR response was variable They studied 4 unanesthetized dogs with denervated hearts and observed an increase in HR which indicates that Nethalide has direct stimulating actions on the heart Koch Weser[4] also found that Nethalide had a weakly positive chronotropic effect on isolated cat atrial tissue An additional

mechanism by which the HR may increase in response to Nethalide despite blockade of sympathetic stimuli is through inhibition of the parasympathetic nervous system as demonstrated by Ledsome and associates[9] Blockade of peripheral vagal activity was shown by James and Nadeau[10] by direct perfusion of the sinus node with Nethalide The failure of atropine to significantly increase HR in our experiments also suggests that Nethalide had blocked vagal activity prior to the administration of atropine The relative contribution of these mechanisms to the observed increase in HR is unknown and the role of each may vary in different experimental conditions

Calculated systemic resistance decreased significantly in this study after Nethalide was infused and since arterial pressure tended to fall despite an increase in cardiac output it can be inferred that vasodilatation had occurred A similar conclusion was reported by Black and Stephenson[7] and led to a trial of Nethalide as a hypotensive agent[11] Vasodilatation probably caused the conspicuous flush noted in some animals and has been documented in studies of peripheral blood flow by Lowe and Robinson[1] This is most likely a non adrenergic effect of the drug since blockade of beta sympathetic activity in peripheral vessels should cause arterial constriction and venodilatation[12]

The mechanisms by which Nethalide influences cardiac output are complex and could include effects of the drug on factors such as initial myocardial fiber length contractile performance and afterload which are difficult to define separately We have considered that the equivalent in the intact animal to afterload as studied in isolated papillary muscle preparations is end systolic force and that mean circumferential shortening rate is a reflection of inotropic responsiveness Mean circumferential shortening rate after Nethalide was not significantly different from control values and the relationship between shortening velocity and both end systolic force and end diastolic volume was also normal By these criteria the drug does not affect the contractile state of the myocardium A negative inotropic effect is suggested however by the influence of the drug on the end systolic force per unit of end systolic circumference A reduction in afterload by a peripheral mechanism (e g arterial vasodilatation) should result in the development of less end systolic force but at a dimension defined by the normal force to end systolic circumference relationship (Fig 1) since all of the values obtained after Nethalide lie below the regression line for the control data a negative inotropic influence is inferred because less force is generated per unit of circumference A negative inotropic effect is not incompatible with the findings that the ESD/EDV ratio decreased and stroke volume and cardiac output increased These results indicate that the preponderant effect of the drug is vasodilatation and that enhanced ventricular emptying occurred secondary to the fall in afterload despite a negative inotropic effect No consistent variation occurred in either stroke work index or EDV that would implicate the Frank Starling mechanism in the hemodynamic events after Nethalide

Propranolol a newer beta blocking drug has superseded Nethalide for clinical studies because it has fewer unpleasant side effects when given to patients Unlike Nethalide it apparently does not have a carcinogenic effect in mice[13] The original report by Black and associates[14] claimed that propranolol had essentially the same pharmacologic properties as Nethalide and was 10 times as potent A dose of 0 5 mg per kilogram was used in the present investigation because it is one tenth of the amount of Nethalide given and because this quantity has been shown to abolish the heart rate response of dogs to sympathetic nerve stimulation[9] Contrary to previous reports data from the present study demonstrate that the two drugs cause different hemodynamic changes when given in a 10 1 ratio to anesthetized intact dogs

Propranolol did not change cardiac output HR or SV but raised the ESV EDV ratio and left ventricular end diastolic pressure All animals given propranolol showed an increase in left ventricular transmural pressure associated with variable changes in EDV this is best explained by a decrease in diastolic distensibility

of the ventricle although we have not eliminated the possibility that intrapericardial pressure increased It is possible that this alteration is due to the effects of adrenergic blockade on the ventricular myocardium which would be consistent with the observation by Hefner and associates[16] that epinephrine a beta receptor stimulator increased diastolic distensibility Mitchell Linden and Sarnoff[17] however found that adrenergic activity did not change the pressure fiber length characteristics of the ventricle An alternative explanation is that the drug exerts a direct effect on the mechanical properties of heart muscle by decreasing the compliance of either the contractile or parallel elastic elements

Mean circumferential shortening rate is a function of end systolic force (which includes in part total peripheral resistance) EDV and the contractile state of the myocardium The administration of propranolol caused a significant increase in end systolic force which by itself should reduce shortening velocity as defined by the normal force velocity relationship (regression line in Fig 3) Virtually all of the values after the drug were lower than expected which could be accounted for by either a decreased EDV or a negative inotropic effect Since mean circumferential shortening rate was also lower than normal at any given EDV (Fig 2) propranolol must have had a negative inotropic influence

The evidence favoring a negative inotropic response to the drug occurred while there was a heightened end systolic force at any end systolic circumference The alteration in force derived by multiplying end systolic tension and end systolic circumference is due to changes in tension because variations in circumference alone would not deviate from the expected force circumference relationship (Fig 1) Two factors contribute to end systolic muscle tension an active component dependent on the intensity of muscle fiber contraction and a passive component determined by the elasticity of the muscle (series elastic element) An increase in either would augment end systolic tension We cannot distinguish between these two with certainty but in view of the evidence which favors a negative inotropic effect of the drug and the unlikely possibility of recruitment of more muscle fibers a decreased compliance of the series elastic element is more probable It is possible therefore that propranolol affects both series and parallel elastic elements throughout the cardiac cycle

Our data apply only to the effects of Nethalide and propranolol in intact dogs anesthetized with chloralose urethane The degree of sympathetic stimulation in these animals was variable and in some instances (Dogs No 7 and 14) was presumably high It can be inferred that sympathetic activity was not inordinate during the control periods in most dogs given propranolol because after beta adrenergic blockade there was no decrease in heart rate and only contractility and elasticity were affected It is conceivable that different thresholds exist at which propranolol influences various modalities of beta receptor activity however the responses could also be due to a direct effect of the drug on the heart and our data are insufficient to distinguish between these possibilities

## Summary

The hemodynamic effects of two beta blocking drugs were evaluated in intact dogs anesthetized with chloralose urethane Nethalide (5 mg per kilogram intravenously in 15 minutes) significantly increased cardiac output heart rate and stroke volume and decreased end systolic volume/end diastolic volume ratio and systemic vascular resistance The decrease in calculated end systolic force per unit of end systolic circumference suggests a negative inotropic effect The preponderant effect of the drug was arterial dilatation which cannot be explained by beta adrenergic blockade Better ventricular emptying was probably secondary to decreased afterload since end diastolic volume did not change

The chief site of activity of propranolol (0 5 mg per kilogram intravenously in 5 minutes) was on the myocardium left ventricular end diastolic pressure increased without a change in end diastolic volume, which indicates that diastolic distensibility was reduced In addition mean circum

ferential shortening velocity decreased which suggests a negative inotropic effect end diastolic volume and stroke work were unchanged and end systolic force per unit of end systolic circumference increased The latter is perhaps due to an increased contribution of elasticity to end systolic tension We do not know whether these results are due to inhibition of beta adrenergic activity or to direct effects on the myocardium

We are grateful to Dr Alex Sahagian Edwards of Ayerst Laboratories for the supplies of Nethalide (Alderlin) and propranolol (Inderal) and to Mr Arnold Rosen for technical assistance

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# Chronic pharmacologic treatment of experimental hypoxic pulmonary hypertension

## With observations on rate of change in pulmonary arterial pressure

*John H. K. Vogel, M.D.**
*Daniel Cameron***
*Gail Jamieson, B.A.****
*Denver, Colo.*

Previous reports from this laboratory have shown that ligation of the left pulmonary artery in the newborn calf results in progressive pulmonary hypertension when performed at an altitude of 5,000 feet[1] but not at sea level; thus a preparation was produced for the study of hypoxic pulmonary hypertension. In this paper a detailed evaluation of chronic pharmacologic therapy in such a preparation is reported and contrasted with acute treatment.

### Methods

Ligation of the left pulmonary artery was performed in a newborn calf within 24 hours of birth. The animal was premedicated with 0.4 mg. of atropine subcutaneously. A plastic bag was placed over its head and induction was accomplished with a high flow rate of 4 per cent halothane† and 4 liters per minute of both oxygen and nitrous oxide. Within 4 minutes it was possible to intubate the animal, after which the animal was maintained with a 0.5 per cent concentration of halothane. After the chest had been opened it was possible to maintain the animal with 250 c.c. of both nitrous oxide and oxygen without halothane. Upon completion of the surgical procedure the animal was awake within 5 minutes. The animal was then promptly returned to the Research Farm. The mother's colostrum and 50 c.c. of anti coli enteritidis Pasteurella serum‡ were given to the animal.

Serial right heart catheterizations were performed percutaneously via an external jugular vein with either a PE 60 tubing or a No. 6F smooth bore catheter. Systemic arterial blood and pressures were obtained by needle puncture of the descending aorta through the last intercostal space on the left, using a 6 inch, 18 gauge, thin walled needle. All studies were performed with the animal standing erect in a stanchion without premedication.[1]

Five months after surgery the animal

From the Cardiovascular Laboratory, University of Colorado Medical Center, Denver, Colo.
Supported in part by the American Heart Association (Grant 63 G 150) and The Idaho Heart Association.
Received for publication Oct. 5, 1966.
*Assistant Professor of Medicine and Associate Director, Clinical Cardiovascular Laboratory, University of Colorado Medical Center. Address: University of Colorado Medical Center, 4200 East Ninth Ave., Denver, Colo. 80220.
**Supervisor of Animal Chamber, Research Farm, University of Colorado Medical Center.
***Research Associate, Cardiovascular Laboratory, University of Colorado Medical Center.
†Kindly supplied as Fluothane by Ayerst Laboratories, New York, N. Y.
‡Haver Lockhart Laboratories, Kansas City, Mo.

was started on a program of daily intravenous acetylcholine* and nasal oxygen 5 to 10 liters per minute. This program was continued for 13 days. The acetylcholine was administered in a continuous manner using a micro-flow Sage pump† which was taped to the animal's head. After treatment was discontinued, serial observations of pulmonary arterial pressure were obtained over a 7 week period. The calf was then placed in a 1 ton van and transported to sea level (Houston, Texas). This trip required 25 hours. Right heart catheterization was performed at 1, 16, and 40 hours and 1 week and 4 months after arrival at sea level. Serial electrocardiograms were also obtained.

Pressures were obtained using a P23db Statham strain gauge energized by an Electronics for Medicine amplifier and recorded on an Electronics for Medicine photographic recorder. Mean pressures were obtained electronically. The oxygen content and capacity of samples of blood were obtained by the method of Van Slyke and Neill. Blood pH was determined by the micro technique of Siggaard-Andersen and associates[2] and oxygen and carbon dioxide tensions were measured directly with electrodes at body temperature using the Radiometer‡ apparatus. Carbon-dioxide tension was checked by the Astrup micro tonometer technique[3] as well as by the Van Slyke method using the chart of Sendroy.

**Results**

Two weeks after surgery, mean pulmonary arterial pressure was 33 mm Hg which is in the normal range for a 2 week old calf.[4] As shown in Fig. 1 and Table I, there was a progressive rise in mean pulmonary arterial pressure from 53 mm Hg at 2 months to 120 mm Hg at 5 months. This was associated with a decrease in cardiac output as evidenced by widening of the arteriovenous oxygen difference to 7.22 volumes per cent from 5.56. $Pa_{O_2}$ was essentially unchanged being 59.0 mm Hg. The response of the calf to various combinations of acetylcholine and oxygen was then determined as shown in Fig. 2. With the administration of 44 per cent oxygen by mask, resulting in a $Pa_{O_2}$ of 114.8 mm Hg, mean pulmonary arterial pressure was reduced from 126 to 95 mm Hg; it returned promptly to control levels after the discontinuation of oxygen. With an infusion of acetylcholine at a rate of 4 mg. per minute over a 3 minute period, mean pulmonary arterial pressure was reduced from 120 to 75 mm Hg, whereas aortic pressure decreased slightly from 120 to 105 mm Hg. Five minutes after discontinuation of acetylcholine, pulmonary arterial pressure had returned to control levels. Acetylcholine was then readministered in a dose of 1.5 mg. per minute over a 17 minute period; this resulted in a decrease in mean pulmonary arterial pressure from 122 to 80 mm Hg and in mean aortic pressure to 115 mm Hg. Mean pulmonary arterial pressure then rose slowly, being 100 mm Hg at 1 minute after acetylcholine was discontinued and 109 mm Hg an hour later. The administration of 100 mg. of tolazoline into the pulmonary artery was without effect on pulmonary arterial pressure (not shown on the chart).

Acetylcholine was then administered at a rate of 1 mg. per minute over a 90-minute period. Mean pulmonary arterial pressure was reduced from 109 to 90 mm Hg. Of interest is the fact that 30 minutes after acetylcholine was discontinued, mean pulmonary arterial pressure had remained unchanged at 90 mm Hg; with readministration of acetylcholine in a dose of 1.0 mg. per minute, mean pulmonary arterial pressure was reduced to 60 mm Hg, and with the addition of nasal oxygen at 10 liters per minute to [illegible]5 mm Hg. When acetylcholine was discontinued, mean pulmonary arterial pressure rose to [illegible] mm Hg and with discontinuation of oxygen there was a prompt rise to 107 mm Hg. Forty-five minutes later, acetylcholine and oxygen again effected a fall in mean pulmonary arterial pressure from 107 to 55 mm Hg, which was associated with little change in mean aortic pressure from 107 to 10[illegible] mm Hg.

Subsequently, acetylcholine and oxygen were given intermittently for 17 additional days. In Table II the acetylcholine and oxygen treatment is detailed over this

*Kindly supplied by Merck and Co.
†Model 1 2 [illegible]
‡Radiometer, Copenhagen, Denmark.

Table I Physiologic

| Cath No | Procedure | | Mean pressures (mm Hg) | | | | O sat (%) | | C | I | I | pH | pH | Hgb (Gm %) | Heart rate |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | RA | PA | A | R dev | [illegible] | [illegible] | | | | | | | |
| 1 | Rest (2 wk old) | May 14 1961 | 4 | 33 | 114 | 14 | 61 6 | 93 7 | 5 56 | 59 2 | | 7 339 | 7 334 | 15 9 | |
| 2 | Rest | June 2 1961 | 3 | 50 | 142 | | 57 9 | 95 4 | 5 92 | 49 8 | 39 2 | 7 391 | 7 354 | 13 6 | 100 |
| | 3 min nasal $N_2$ | | | 75 | | | 47 6 | 80 1 | 6 00 | 36 8 | 35 1 | 408 | 361 | 13 2 | 170 |
| 3 | Rest | July 1 1961 | 3 | 51 | | | 48 0 | 93 9 | 5 0 | | | | | 11 4 | 100 |
| | 2 min 13 per cent $O_2$ (mask) | | | 90 | | | | 61 6 | | | | | | 11 6 | 170 |
| 4 | Rest | Sept 24 1961 | 3 | 92 | 1 0 | 11 | 54 | 96 5 | 5 56 | 63 0 | 41 2 | 7 441 | 7 390 | 12 3 | 110 |
| | 5 min 13 per cent $O_2$ (mask) | | | 145 | 105 | 14 | 38 2 | 61 9 | | 36 0 | 41 9 | 7 452 | 7 410 | 12 | 200 |
| | 4 min 44 per cent $O_2$ (mask) | | | 65 | | | 65 6 | 93 6 | 5 31 | 113 8 | 55 0 | 343 | 7 339 | 12 3 | |
| | 5 min 44 per cent $O_2$ + 5 per cent $CO_2$ (mask) | | | 76 | 120 | | 65 4 | 97 1 | 5 65 | 1 6 3 | 60 2 | 7 332 | 7 308 | 12 1 | 120 |
| | 1 min after 2 mg of acetylcholine | | | 67 | 90 | 11 | | | | | | | | | |
| 5 | Rest | Oct 3 1961 | 5 | 170 | 135 | | 43 7 | 93 7 | 7 27 | 59 0 | 49 0 | 7 360 | 7 309 | 12 7 | 150 |
| | 5 min 44 per cent $O_2$ (mask) | | | 96 | 137 | | 56 3 | 96 0 | 7 93 | 111 8 | 48 5 | 7 362 | 7 290 | 1 4 | 120 |
| | min acetylcholine 4 mg /min | | | 75 | 105 | | | | | | | | | | |
| | 5 min acetylcholine 1 5 mg /min | | | 50 | 115 | | 51 6 | 91 9 | 6 60 | 59 1 | 41 0 | 7 460 | 401 | 12 6 | |
| Acetylcholine + Nasal $O_2$ Oct 3 through Oct 16 1961 | | | | | | | | | | | | | | | |
| 6 | Rest | October 16 | | 40 | | | | | | | | | | | |
| 7 | Rest | October 19 | | 40 | | | | | | | | | | | 96 |
| 8 | Rest | October 19 | | 41 | | | 61 0 | | | | | | 7 393 | | 96 |
| | 3 min 13 per cent O (mask) | | | 119 | | | 37 0 | | | | | | 7 390 | | 100 |
| 9 | Rest | October 20 | | 58 | | | | | | | | | | | 200 |
| 10 | Rest | October 21 | | 55 | | | | | | | | | | | 100 |
| 11 | Rest | October 22 | | 55 | | | | | | | | | | | 95 |
| 12 | Rest | October 23 | | 72 | | | | | | | | | | | 95 |
| 13 | Rest | October 24 | | 50 | | | | | | | | | | | 90 |
| 14 | Rest | October 26 | 4 | 48 | | | | | | | | | | | 100 |
| 15 | Rest | October 28 | | 41 | | | 55 4 | | | | | | 7 370 | | 100 |
| | 4 min nasal $O_2$ 10 l /min | | | 49 | | | 51 0 | | | | | | 7 373 | | 100 |
| 16 | Rest | October 30 | 5 | 1 | | | 51 0 | | | | | | 7 315 | | 96 |
| 17 | Rest | November 2 | 7 | 33 | | | 56 7 | | | | | | | | 100 |
| 18 | Rest | November 5 | 4 | 55 | | | | | | | | | | | 92 |
| 19 | Rest | November 10 | 5 | 62 | | | | | | | | | | | 90 |
| 20 | Rest | November 20 | 3 | 73 | | | | | | | | | | | 92 |
| 21 | Rest | November 25 | | 55 | | | | | | | | | | | 130 |
| 22 | Rest | December 7 | 9 | 122 | | | 49 5 | | | | | | 7 469 | | 150 |
| | 9 min nasal $O_2$ 12 l /min | | | 93 | | | 45 2 | 89 1 | 7 65 | 55 2 | 39 4 | 7 465 | 401 | 12 5 | 190 |
| To Houston Dec 5 to Dec 9 1964 | | | | | | | 54 5 | 98 3 | 7 33 | 90 1 | 49 9 | 7 400 | 375 | 12 0 | 140 |
| 23 | Rest | December 9 | 3 | 75 | 112 | | | 95 7 | | | | | | | |
| 4 | Rest | December 10 | | 35 | | | | | | 94 0 | 35 0 | 7 453 | 7 408 | | 103 |
| | 2 min 8 per cent $O_2$ in bag | | | 5 | | | 63 4 | 95 6 | 5 20 | 90 0 | 42 5 | 7 451 | 7 411 | 12 2 | 96 |
| 25 | Rest | December 11 | 4 | 35 | 122 | | | 61 0 | | 46 0 | 35 2 | 7 436 | | | 170 |
| | 5 min 8 per cent $O_2$ in bag | | | 7 | | | 53 8 | 91 0 | 6 20 | | 38 0 | 7 490 | 4 0 | 11 3 | 96 |
| 6 | Rest | December 17 | | 34 | | | | 98 0 | | | | 7 500 | 7 456 | | 100 |
| | 2 min 8 per cent $O_2$ in bag | | | 50 | | | | | | | | | | | 95 |
| 27 | Rest | April 8 1963 | | 10 | | | | | | | | | | | |

Fig. 1 Mean pulmonary arterial pressure is plotted against time. Each star represents an individual observation. The upright arrows indicate response to acute hypoxia and the downward arrows represent the response to the acute administration of mixtures high in oxygen.

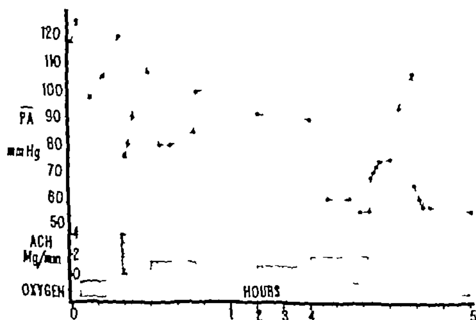



Fig. 2 Response of mean pulmonary arterial pressure to acetylcholine (Ach) and oxygen. Note progressively lower pressure with repeated pharmacologic treatment.

*Table II Summary of pharmacologic treatment in Calf No 36*

| Date (1964) | Treatment | Mean PA pressure (mm Hg) | |
|---|---|---|---|
| | | Before | During or After |
| October 3 | Acetylcholine 1 mg min 1 00 P M to 3 00 P M | 120 | 60 |
| | Oxygen 10 L /min 8 00 P M to 6 00 A M October 4 | 64 | 50 |
| October 4 | Acetylcholine 8 20 A M ( ) tube out | 52 | 40 |
| | Oxygen 10 L min 5 30 P M to 6 00 A M October 5 | — | 32 |
| October 5 | Acetylcholine 1 5 mg /min 9 25 A M to 4 30 P M | 32 | 50 |
| | 1 5 mg /min 6 15 P M to ? | 47 | 40 |
| | Oxygen 5 L /min 5 45 P M to 7 00 A M October 6 | 58 | 47 |
| October 6 | Acetylcholine 1 1 mg /min 6 30 P M to 10 00 A M October 7 | 45 | 47 |
| | Oxygen 7 L /min 6 00 P M to 8 00 A M October 7 | 55 | 43 |
| October 7 | Oxygen 7 L /min 9 30 P M to | 52 | 45 |
| October 8 | Oxygen 7 L /min 8 00 P M to 7 00 A M October 9 | 47 | 41 |
| October 9 | No treatment | | |
| October 10 | Acetylcholine 1 5 mg /min 8 30 P M to 3 00 A M October 11 | — | — |
| | Oxygen 7 L /min 8 00 P M to 12 00 P M October 11 | 47 | 4 |
| October 11 | Acetylcholine 1 5 mg /min 7 15 to 9 00 A M October 12 | 42 | — |
| | Oxygen 7 L /min 7 30 P M to 10 30 A M October 12 | — | — |
| October 12 | Acetylcholine 1 5 mg /min 1 00 P M to 7 00 A M October 13 | — | — |
| | Oxygen 7 L min 3 30 P M to 8 00 A M October 13 | — | — |
| October 13 | Acetylcholine 1 5 mg min 12 00 P M to 10 00 P M | 33 | — |
| | Oxygen 7 L /min 3 30 P M to 8 00 A M October 14 | — | 37 |
| October 14 | Acetylcholine 1 5 mg min 12 45 P M to 7 00 A M October 15 | 37 | — |
| | Oxygen 7 L /min 3 00 P M to 9 00 A M October 15 | — | — |
| October 15 | Acetylcholine 1 5 mg /min 8 30 P M to 4 00 P M October 16 | 40 | — |

12 day period Mean pulmonary arterial pressure was 52 mm Hg on the second day before treatment was continued There was a further slow progressive decrease in mean pulmonary arterial pressure to 33 mm Hg after 11 days of therapy On the last day of treatment mean pulmonary arterial pressure was 40 mm Hg This was associated with an increase in mixed venous saturation to 64 per cent from a low value of 43 7 per cent prior to therapy suggesting a narrowing of the arteriovenous oxygen difference and increased cardiac output

After discontinuation of therapy there was a slow rise in mean pulmonary arterial pressure to 48 mm Hg at 2 weeks and to 122 mm Hg at 7 weeks This was associated with a rise in mean venous pressure to 10 mm Hg and a reduction in cardiac output as manifested by widening of the arteriovenous oxygen difference to 7 65 volumes per cent $Pa_{O_2}$ was 58 2 mm Hg and unchanged from prefailure values Clinically the animal was in marked distress with severe dyspnea on minimal exertion mild scours distended neck veins and nose breathing

Fig 3 shows the time course in relationship to altitude of the trip from Denver to Houston One hour after arrival at Houston mean pulmonary arterial pressure was 75 mm Hg and $Pa_{O_2}$ had increased to a normal sea level value of 94 mm Hg It may be noted from Fig 3 that the animal had then been below 1 000 feet in altitude for approximately 11 hours Sixteen hours after arrival at Houston mean pulmonary arterial pressure was 38 mm Hg and after 40 hours 35 mm Hg Mean venous pressure decreased to 4 mm Hg Sixteen hours after arrival the arteriovenous oxygen difference had narrowed to a normal value of 5 2 volumes per cent Clinically the animal was markedly improved being able to stand considerable exertion without obvious dyspnea One week later mean pulmonary arterial pressure was 34 mm Hg and at 4 months 40

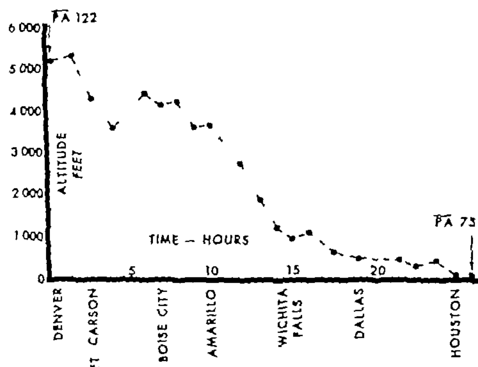



Fig 3 Chart illustrating the rate of change in altitude during trip from Denver to Houston

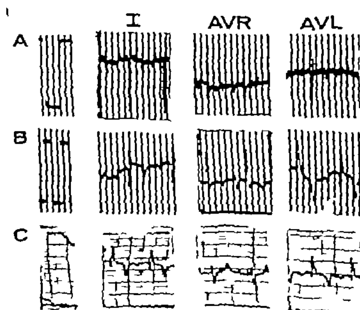



Fig 4 Serial electrocardiograms in Calf No 36 taken to sea level *A* Dec 9 1964 mean PAP = 75 mm Hg *B* Dec 11 1964 mean PAP = 35 mm Hg *C* Dec 1[illegible] 1964 mean PAP = 34 mm Hg Note significant leftward shift of QRS axis occurring within 8 days after arrival at sea level *The* first tracing (Dec 9 1964) taken 1 hour after arrival in Houston is identical with the tracing obtained immediately prior to leaving Denver (STD = 1 m[illegible])

mm Hg Moreover serial electrocardiograms revealed a progressive leftward shift of the QRS axis (Fig 4)

**Discussion**

In our previous study it was shown that ligation of the left pulmonary artery in the newborn calf resulted in progressive pulmonary hypertension when performed in Denver at an altitude of 5 000 feet[1] Subsequent attempts to reproduce these results at sea level were unsuccessful[2] However when calves in which ligation of the left pulmonary artery had been performed at sea level were transported to Denver progressive pulmonary hypertension developed This indicated that whereas the increased pulmonary blood flow consequent to ligation of the left pulmonary artery at sea level was an insufficient stimulus to produce pulmonary hypertension the addition of the lower $P_{AO_2}$ of 5 000 feet provided the necessary stimulus for the production of progressive pulmonary hypertension Thus at an altitude of 5 000 feet ligation of the left pulmonary artery in the newborn calf provides a useful model for the study of hypoxic pulmonary hypertension

Furthermore it has been shown that infants under 2 years of age with ventricular septal defects and pulmonary hypertension who reside at an altitude of 5 000 feet have nearly twice the pulmonary vascular resistance of those residing at sea level The difference in resistance was thought to be attributable to greater pulmonary blood flow at sea level because of the higher $P_{AO_2}$ Consequently there is additional evidence in human subjects with underlying disease affecting the pulmonary circulation that the mild hypoxia of 5 000 feet may further alter pulmonary vascular resistance

By contrast in normal subjects mean pulmonary arterial pressure is only slightly increased between sea level and 5 000 feet being 12 and 16 mm Hg respectively but at an altitude of 10 150 feet the mean pressure is significantly higher being 25 mm Hg[4] Similarly in normal calves there is little difference between pulmonary arterial pressure at sea level and that at 5 000 feet but if the animals are taken to 10 000 feet pulmonary hypertension develops with mean pulmonary arterial pressures of 45 mm Hg after 2 months and 60 mm Hg by 6 months[5] Moreover it has been shown that progression of the pulmonary hypertension can be accelerated by chronic exposure to an altitude of 12 700 feet[6]

The reversibility of such hypoxic pulmonary hypertension in both normal man and calves has also been reported Thus in a 16 year old girl who had a resting mean pulmonary arterial pressure of 44 mm Hg at 10 150 feet a mean pressure of 17 mm Hg was recorded 11 months after she had gone to sea level[7] In addition Peñaloza and associates[8] reported in 11 subjects a reduction in mean pulmonary arterial pressure from an average value of 24 mm Hg at 14 200 feet to 12 mm Hg 2 years after their arrival at an altitude of 500 feet In neither of the above mentioned studies was it possible to assess the rapidity of the reduction in pulmonary arterial pressure because of the long time intervals Of interest in this regard is a report by Kuida and associates[9] on serial studies in calves with hypoxic pulmonary hypertension and right heart failure (brisket disease) at an altitude of 4 500 feet Studies were performed 2 days after arrival in Salt Lake City and then at 5 day intervals Initial mean pulmonary arterial pressures ranged from 45 to 115 mm Hg All animals experienced a reduction in pulmonary arterial pressure but the time sequence of catheterization did not allow a precise evaluation of the rate of fall in pressure since studies were not carried out prior to leaving high altitude or immediately upon arrival in Salt Lake City Furthermore there are no data on the rate of change in pressure in animals suffering from brisket disease which have been taken to sea level

That a rapid decrease in pulmonary arterial pressure is possible however is suggested by the recent report of Emmanouilides and associates[10] who showed that in the human newborn infant at sea level the major decrease in pulmonary arterial pressure occurred within 24 hours after birth Moreover Averill and associates[11] have noted a similar rate of change in newborn puppies studied at an altitude of 5 000 feet The present study has shown

the rapidity with which hypoxic pulmonary hypertension may decrease upon exposure of the subject to the pO present at sea level Thus within 1 hour after arrival at Houston mean pulmonary arterial pressure had decreased to 75 mm Hg from a value of 122 mm Hg in Denver and after 16 hours, to 38 mm Hg

Whether these rapid and extensive changes in pressure were due to anatomic changes in the pulmonary arteries and/or relief of vasoconstriction remains to be determined In previous studies it was shown that when cattle with brisket disease were given oxygen to breathe while still at high altitude only a slight fall in pulmonary arterial pressure was achieved [6] This failure to reduce pressure further was attributed to the presence of anatomic changes within the pulmonary arteries whereas the additional elevation of pressure which was alterable by oxygen was attributed to vasoconstriction If the changes in pressure observed in the present study were due in large part to anatomic alterations this would suggest that within hours marked alterations may occur in cytoplasmic mass That anatomic changes (medial hypertrophy) may be present in normal subjects residing above an altitude of 10 000 feet has been shown by Naeye[31] and Arias Stella and Saldaña [32] However that vasoconstriction played a role was evidenced by the acute response to pharmacologic agents Moreover postmortem pulmonary arteriography has suggested a considerable degree of vasoconstriction in addition to medial changes (Fig 5) The fact that pressure could be altered so dramatically after but hours of treatment suggests that some degree of reversible contracture was associated with the vasoconstriction and anatomic changes Further studies are now in progress to evaluate the histologic changes appearing during these rapid changes in pressure The rapid decrease in pulmonary arterial pressure noted in this study upon descent to lower altitude is in contrast to the slower rate of increase in pulmonary arterial pressure observed upon ascent to high altitude which takes weeks to months to develop [4 7 14]

The calf in the present study developed progressive pulmonary hypertension during a time course similar to that previously re

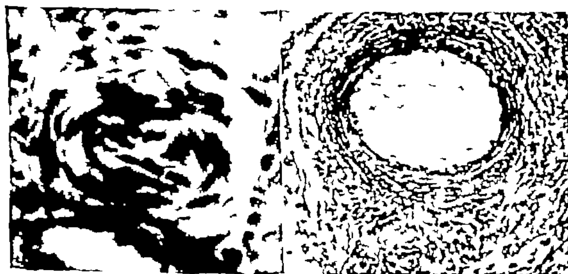


Fig 5 *Left* Muscular pulmonary artery from right upper lobe of calf with ligation of the left pulmonary artery which died with heart failure and progressive pulmonary hypertension *Right* Muscular pulmonary artery from right lower lobe of same animal Vessel has been injected with Micropaque and gelatin Note that with distention of the vessel the medial layer is much less impressive than in the uninjected contracted vessel shown at left These studies suggest that in addition to the increased size and number of medial cells vasoconstriction plays an important role in the development of pulmonary hypertension

ported[1] In that study it was also shown that the acute administration of intravenous acetylcholine was effective in reducing pulmonary hypertension in calves as was the administration of mixtures high in oxygen[1] Moreover it was shown that the combination of acetylcholine and oxygen was more effective than either alone It has also been shown in normal individuals residing at an altitude of 10 000 feet that a combination of tolazoline and oxygen was more effective than either agent given separately[4] Tolazoline was employed in the present study without effect and previous papers have noted that it is ineffective in the calf[1,7]

Of interest was the demonstration that the results of acute administration of either acetylcholine and/or mixtures high in oxygen were not indicative of the responses that could be obtained with chronic administration Thus when the animal achieved a resting mean pulmonary arterial pressure of 120 mm Hg at 5 months of age acute administration of oxygen resulted in a decrease to 96 mm Hg and of acetylcholine to 75 mm Hg However after a 2 hour infusion of acetylcholine plus readministration of oxygen mean pulmonary arterial pressure was reduced to 55 mm Hg After 11 days of intermittent chronic therapy with acetylcholine and nasal oxygen mean pulmonary arterial pressure reached a low of 33 mm Hg Furthermore after treatment was discontinued 7 weeks were required before pulmonary arterial pressure returned to the control level of 120 mm Hg Again acute administration of oxygen did not reflect the potential reduction possible in that mean pulmonary arterial pressure decreased from 122 to but 93 mm Hg in association with an increase in $P_{IO_2}$ from 58 2 to 90 mm Hg However within 1 hour after arrival in Houston mean pulmonary arterial pressure had decreased to 75 mm Hg in association with a normal sea level $Pa_{O_2}$ of 94 mm Hg As shown in Fig 3 the animal had been below 1 000 feet for approximately 11 hours Sixteen hours after arrival in Houston mean pulmonary arterial pressure had decreased to 38 mm Hg This further decrease in pressure was not associated with any further change in $Pa_{O_2}$ Cardiac function was improved as manifested by a decrease in venous pressure and an increase in cardiac output Clinically the animal's exercise tolerance was markedly improved

Thus the results of this study as well as observations in normal man have shown that hypoxic pulmonary hypertension is in large part reversible and indicate the feasibility of chronic pharmacologic treatment of hypoxic pulmonary hypertension It has been reported that chronic observation of pulmonary arterial pressure at the bedside is a feasible procedure and relatively easily performed[15] A number of clinical situations would appear to be susceptible to chronic treatment and observation as performed in this study Studies in children with hypoxic pulmonary hypertension and cystic fibrosis have shown the feasibility of acute and chronic therapy with intravenous tolazoline for the reduction of pulmonary hypertension[16] In the same study the importance of observing the effects of sleep on pulmonary arterial pressure was also shown Chu and associates[17] have shown that the repeated administration of acetylcholine is effective in children with respiratory distress syndrome and more recently Cotton[18] has shown the usefulness of tolazoline in this syndrome with benefit presumably resulting from relief of pulmonary arterial vasospasm Naeye and Blanc[19] have reported a syndrome characterized by premature closure of the foramen ovale associated with normal development of the left ventricle in which severe pulmonary hypertension appeared to be responsible for death Repeated administration of tolazoline to such infants might be life saving Hypoxic pulmonary hypertension is a significant problem in patients with hypoventilation resulting from restrictive chest disease obesity or chronic bronchitis and it is suggested that chronic pharmacologic therapy may prove to be useful in such patients[14,20] Recently we studied a patient with pulmonary hypertension associated with obesity and hypoventilation in whom ethamivan appeared to be effective in improving ventilation and decreasing the pulmonary hypertension[1] Furthermore in children with congenital heart disease and reactive pulmonary hypertension chronic therapy

both preoperatively and postoperatively may be beneficial

## Summary

In this study the effect of chronic pharmacologic treatment of hypoxic pulmonary hypertension was evaluated The responses to *acute* pharmacologic treatment were considerably less than the responses to chronic treatment These results illustrate the feasibility of chronic pharmacologic treatment for the reduction of hypoxic pulmonary hypertension Furthermore these studies confirm the importance of vasoconstriction in chronic hypoxic pulmonary hypertension and the rapidity with which pulmonary arterial pressure may decrease when the hypoxic stimulus is blocked or removed

We wish to thank Dr Daniel McNamara and Dr J D McCrady for making possible the studies at Baylor University Hospital, Dr Harry Page for helping with the catheterization studies and Mrs Audrey VanCamp and Mrs Marilyn Leek for typing the manuscript

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# Physiologic evidence concerning the re-entry hypothesis for ectopic beats

*Andrew G. Wallace, M.D.*
*Robert J. Mignone, B.S.*
*Durham, N. C.*

Premature beats, particularly those of ventricular origin, are a commonly encountered abnormality of cardiac rhythm. Although many of the pertinent factors which may account for these disturbances have been elucidated from microelectrode studies, a demonstration of actual mechanisms in the intact heart is lacking.

The phenomenon of coupling indicates that this type of extrasystole probably does not arise *de novo* from an independently discharging pacemaker. Rather, the coupled beat appears to be initiated in some way by activity of the preceding cycle.[1] The concept of re-entry has been proposed to account for coupled extrasystoles. According to this hypothesis, recovery of excitability is presumed to occur in a nonuniform manner, so that a succeeding impulse can initially be refracted from areas which have not fully recovered, but later enter these areas during the relative refractory period when propagation is slow. If conduction is sufficiently slow, adjacent myocardium could then recover and the slowly propagating impulse could emerge from the depressed zone to initiate the extrasystole.

The studies described in this report were designed to test the re-entry hypothesis by creating a discrete and reversible area of nonuniform recovery within the intact ventricle. A focal reduction in temperature was selected because it seemed to be likely that this alteration would result in a substantial dispersion of refractory periods at the junction between warm and cold muscle. The consequences of this intervention were found to include marked local alterations in recovery and conduction, intramural block, and re-entry.

## Methods

Studies were performed on 10 healthy dogs which weighed 11 to 15 kilograms. The animals were anesthetized with thiamylal, 10 to 20 mg. per kilogram, and ventilated with a Harvard respirator. A mid-sternal thoracotomy was performed and the pericardium was used to cradle the heart. The sinus node was crushed to slow the intrinsic heart rate. Pacing wires were attached to the right atrial appendage and connected through an isolation unit to a set of Tektronik pulse generators programmed to drive the atrium at a constant rate. A premature atrial beat could be introduced at any desired interval after each sixth basic stimulus.

A 2 by 2 cm. silver coil was sutured to

From the Department of Medicine and the Department of Surgery, Division of Thoracic Surgery, Duke University Medical Center, Durham, N. C.
This work was supported in part by a grant from the Walter P. Inman Fund and in part by grants from the United States Public Health Service (HE-06643-05A1 and HE-04987).
Received for publication Oct. 11, 1963.

the anterior surface of the left ventricle Water at varying temperatures could be circulated through the coil at selected rates to produce a local zone of controlled myocardial hypothermia Myocardial temperatures under the coil were measured (to the nearest 0 5 C) at 2 mm intervals between endocardium and epicardium with a needle thermistor advanced through the coil The position of the thermistor was determined at the end of each experiment

A multipolar electrode of the type designed by Scher[3] was advanced through the coil with its tip in the cavity of the left ventricle Care was taken to position the cooling coil so that the electrode did not enter a papillary muscle Wires from the electrode were connected to a switching device which permitted simultaneous bipolar recordings from any two sets of adjacent contacts The electrode consisted of 15 contacts each separated by approximately 1 mm The recording contacts were selected in a manner so that, when the contact nearest the endocardium was negative with respect to its pair a negative deflection was recorded[3] An additional electrode was implanted on the epicardial surface of the right ventricle and used as a reference for timing purposes (Fig 1)

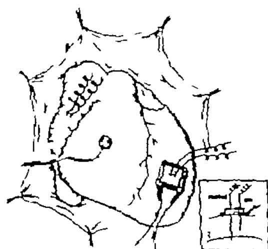


Fig 1 Experimental preparation Pace wires on right atrium Reference electrode on right ventricle Silver cooling coil on left ventricle Insert shows cross section through cooling coil and left ventricle with the Scher electrode and thermistor in position

Signals from each electrode were amplified with special Tektronix 122 A C coupled preamplifiers, displayed on a four channel oscilloscope and recorded on a multichannel Consolidated oscillograph at a paper speed of 8 inches per second The frequency response of the channels used for recording from the Scher electrode was flat from 05 to 1 000 c p s Frequencies below 80 c p s were filtered on the channel used to record from the right ventricular surface electrode in order to sharpen the signal A Lead II ECG also was recorded

The sequence of excitation under the coil was determined by scanning each pair of contacts between endocardium and epicardium and noting the interval between local depolarization and the reference point on the right ventricle This sequence was determined for basic atrial beats ($A_1$) and for premature atrial beats ($A_2$) The multipolar electrode also was used to measure the sequence of recovery at each recording point under the coil following $A_1$ This was accomplished by first noting the time of local activation at each pair of adjacent contacts and then scanning the interval after local depolarization with a 5 msec pulse of twice threshold delivered through the same contacts The effective refractory period at each point was measured as the interval between local depolarization and the time at which a propagated response could be induced by the pulse Observations were made when the myocardium was warm during local cooling and after rewarming

**Results**

Fig 2 shows an example of the effects of the perfusion of ice water on temperatures under the coil At zero flow there was no detectable difference in temperature between the endocardium (0 mm) and the epicardium (10 mm) When ice water was perfused through the coil at a flow of 30 ml per minute there was no change in temperature at the inner 2 mm of the wall but a progressive fall in temperature was observed as the probe was withdrawn to the epicardium resulting in a transmural cardial temperature gradient of 1 C At a flow of 60 ml per minute endocardial temperature

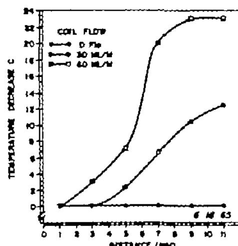



Fig. 2. Effect of perfusing ice water through the coil on transmyocardial temperature gradient. Distance from the cavity is plotted on the horizontal axis. The temperatures are plotted on the vertical axis and expressed as deviations from cavity temperature.

was a more marked fall in temperatures in the mid and outer portions of the wall resulting in a transmyocardial gradient of 23 C. The sigmoid curves relating change in temperature to distance reveal that large temperature gradients existed over distances as short as 2 mm.

An example of the effect of cooling on the sequence of excitation under the coil is shown in Fig. 3. The atrium was paced at a rate of 72 per minute. After each sixth basic beat a premature stimulus was delivered to the atrium which resulted in a propagated ventricular response 350 msec. after the basic ventricular beat. In panel A of Fig. 3 the line described by the solid circles shows the sequence of ventricular activation for the basic beat ($A_1$) prior to cooling. The impulse required 22 msec. to pass from endocardium to epicardium. The spread of activity during the premature supraventricular beat ($A_2$) is described by the line connecting the open circles. Although slight differences were noted during $A_2$, no point varied by more than 3 msec. when compared to $A_1$.

In panel *B* of Fig. 3 the sequence of activity during cooling at 30 ml. per minute is shown. Heart rate and the $A_1$-$A_2$ interval were the same as in panel A. Cooling did not delay $A_1$ at the endocardium or over a distance of 4 mm. into the wall. In the outer half of the wall excitation was delayed by several milliseconds so that the impulse required 31.5 msec. to reach the epicardium. $A_2$ reached the endocardium without delay during cooling, however propagation was markedly slowed in the outer half of the wall so that the interval between endocardium and epicardium was 65 msec.

When ice water was perfused through the coil at flow rates of 30 ml. per minute or greater, there always was some delay of epicardial excitation during $A_1$. However, at flow rates of 15 ml. per minute the sequence of depolarization during $A_1$ was normal. The occurrence of marked intramural delay during $A_2$ as well as the phenomena which will be described subsequently could be produced readily at flow rates of 15 ml. per minute and were not dependent on delayed epicardial excitation during $A_1$.

The effect of cooling on propagation under the coil is demonstrated further by the electrograms shown in Fig. 4. Bipolar records were obtained from the endocar-

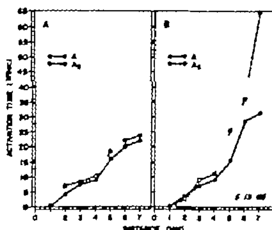



Fig. 3. Effects of perfusing ice water through the coil at 30 ml. per minute on transmyocardial activation times. Distance from the cavity is plotted on the horizontal axis and activation time is plotted on the vertical axis. The electrogram recorded from the first pair of contacts in the endocardial surface (1 mm.) was used as a time reference and arbitrarily designated 0 time. Panel *A* shows observations prior to cooling, and panel *B* shows observations during cooling. Heart rate was 72 beats per minute. The interval between $A_1$ and $A_2$ was 350 msec. See text for further details.

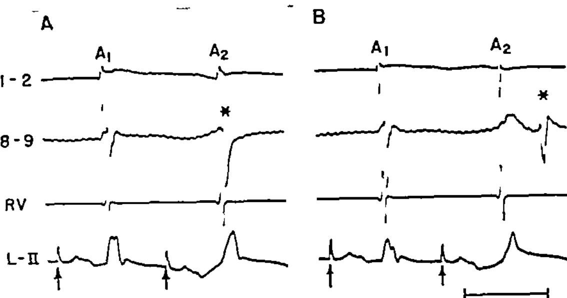



Fig 4 Effects of perfusing ice water through the coil on intramural conduction Panel A shows record prior to cooling and panel B shows record during cooling (15 ml per minute) *1 2* Refers to the electrogram recorded from the first two contacts in the endocardium *8 9* Refers to the electrograms recorded from contacts in the subepicardial zone *RV* Refers to the surface electrogram from the right ventricle *L II* Refers to electrocardiographic Lead II In panels *A* and *B* $A_1$ is the last of a series of six basic supraventricular beats and $A_2$ is a premature atrial response 80 msec after $A_1$ Arrows denote pacing stimuli applied to right atrium Time base = 200 msec

dium (*1 2*) from near the epicardium (*8 9*) and from the epicardial surface of the right ventricle (*RV*) Lead II of the ECG also is shown Panel *A* shows tracings of a basic beat ($A_1$) followed by a premature atrial beat ($A_2$) prior to perfusion of ice water through the coil The interval between depolarization at the endocardium and that at the epicardium was 14 msec during both $A_1$ and $A_2$ Panel *B* shows tracings of a basic beat ($A_1$) and a premature atrial beat ($A_2$) after 10 minutes of perfusion of ice water The $A_1$ $A_2$ interval was the same as in panel *A* During $A_1$ the interval between endocardium and epicardium was 14 msec During $A_2$ depolarization at the endocardium occurred normally but the interval between endocardium and epicardium was prolonged to 100 msec

Intramural delay of $A_2$ occurred only during cooling and could be shown to be a function of the $A_1$ $A_2$ interval Thus when the $A_1$ $A_2$ interval was wide the sequence of excitation for both was identical When the $A_1$ $A_2$ interval was shortened $A_2$ was delayed in the outer portions of the wall as shown in Fig 4 With further shortening of the $A_1$ $A_2$ interval no activity was recorded from the epicardium indicating that propagation of $A_2$ had failed in the intramural portion of the wall On several occasions an $A_1$ $A_2$ interval could be selected at which the block between the endocardium and the epicardium was intermittent or 2 1 in type

Fig 5 shows data from an experiment in which the effective refractory period after $A_1$ was determined at each point under the coil The sequence of recovery before cooling is depicted by the closed circles and that observed during cooling is depicted by the open circles Prior to cooling refractory periods at the different points varied from 218 to 244 msec No consistent differences were noted between the endocardium and the epicardium During cooling the refractory period of the epicardium was prolonged to more than 400 msec Thus cooling not only produced a marked lengthening of the effective refractory period in the outer portion of the wall but also resulted in a

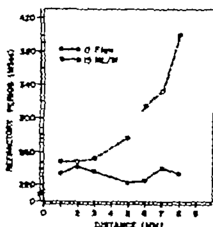



Fig. 5. Effect of perfusion of ice water through the coil of the effective refractory period at seven points between endocardium and epicardium. Distance from the cavity is plotted on the horizontal axis. Effective refractory period after A are plotted on the vertical axis.

substantial increase in the local temporal dispersion of recovery.

In each animal during cooling an $A_1$-A interval could be selected at which A was followed by nonstimulated ventricular extrasystoles. In any given animal the appropriate $A_1$-A interval was one sufficiently short so that A was blocked on transit to the epicardium. When this condition obtained, recording contacts were selected so as to display simultaneously activity from the endocardium and from a point in the wall just proximal to the level of block. In each instance in which a nonstimulated extrasystole was observed, activity in the mid-portion of the wall during A was delayed by more than 90 msec. and was followed by re-excitation of the endocardium coincident with the onset of the nonstimulated ventricular extrasystole. Furthermore, the polarity of the endocardial complex during re-excitation was reversed, indicating that the local direction of spread was from epicardium to endocardium.

Illustrations of the above-mentioned phenomena are presented in Figs. 6 and 7. Although no attempt was made to catalogue the frequency with which nonstimulated responses could be elicited, they could be produced at will in every animal. If the $A_1$-A interval was increased by an amount sufficient to permit A to reach the epicardium, nonstimulated responses were never observed. When the epicardial zone was rewarmed, propagation of A returned to control values and nonstimulated ventricular extrasystoles could not be elicited at any $A_1$-$A_2$ interval.

In 7 of 10 dogs repetitive nonstimulated ventricular extrasystoles followed $A_1$ during cooling. These runs constituted short bursts of ventricular tachycardia, and in each instance the first nonstimulated beat of the run originated from the region of the coil and the endocardial complex indicated inward spread. In 6 of these 7 dogs the run of tachycardia degenerated into ventricular fibrillation. Fibrillation could be converted to normal sinus rhythm in all instances by a single shock applied directly to the heart. Fibrillation was never observed during cooling in the absence of A, and was never observed when the coil was warm regardless of the $A_1$-A interval.

## Discussion

The concept of re-entry finds its greatest support from observations concerning the mechanism of reciprocal rhythm or echoes. Ventricular echoes are beats of supraventricular origin which can be initiated by a properly timed premature ventricular stimulus. The premature response is presumed to arrive at the A-V node when only some cells have recovered from the preceding beat. The impulse enters a group of fibers which has recovered and propagates slowly to the atrium. When the impulse reaches the atrionodal junction, it enters those elements of the node which were not used for retrograde conduction and returns over these fibers to re-excite the ventricle. A re-entry circuit within the node is possible because of the unequal refractory period of adjacent cells and consequent nonuniform recovery of excitability.[4,8]

Schmitt and Erlanger[18] were one of the earliest groups to suggest that re-entry might account for ventricular extrasystoles. They demonstrated that when the central portion of a long strip of muscle was depressed by potassium, an impulse initiated at one end of the strip could be reflected from the depressed zone and return to re-excite the end from which it was initiated. The conditions required to demonstrate this behavior were slow con-

duction with unidirectional block in a part of the muscle. Although the work of Schmitt and Erlanger is quoted often with reference to re-entry, its applicability has been questioned because it seemed to be unlikely that conduction could be slow enough in the intact ventricle to permit re-entry with the usually observed coupling intervals.[1]

The concept of a re-entrant circuit created by nonuniform recovery of excitability has gained credence as a result of

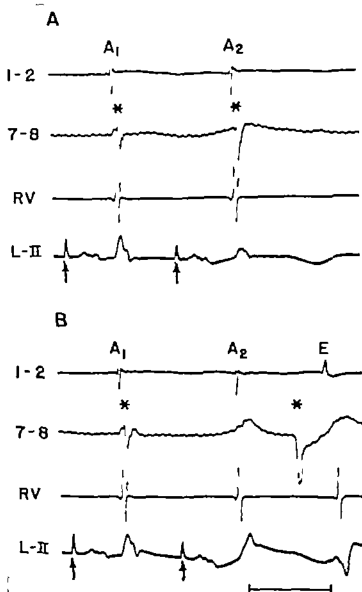



Fig. 6. Re-entrant extrasystoles during cooling. Panel *A* shows record of activity during $A_1$ and $A_2$ prior to cooling. Panel *B* shows record of activity during $A_1$ and $A_2$ while cooling. *1-2* Refers to the electrocardiogram recorded between the first and second contacts in the endocardium. *7-8* Refers to the electrogram recorded from the seventh and eighth contacts. *RV* Refers to the epicardial lead on right ventricle. *L-II* Refers to Lead II ECG. Note that in panel *B* during cooling activity at *7-8* is delayed during $A_2$ by 150 msec and is followed by re-excitation of the endocardium (*E*) which initiates a nonstimulated extrasystole. Time base = 200 msec.

recent experiments by Moe, Mendez and Han.[11] These investigators demonstrated that the refractory period of the right bundle branch often exceeded that of the left bundle branch. When an appropriately timed premature stimulus was applied to the bundle of His, the impulse was blocked in the proximal right bundle branch but propagated to the ventricles over the left bundle branch. After excitation of the ventricles, the right bundle branch was activated retrogradely, and the retrograde impulse returned to re-enter the bundle of His. Although the exact course of the re-entrant pathway could not be established, the circuit required participation of both bundle branches and was established only when the two branches

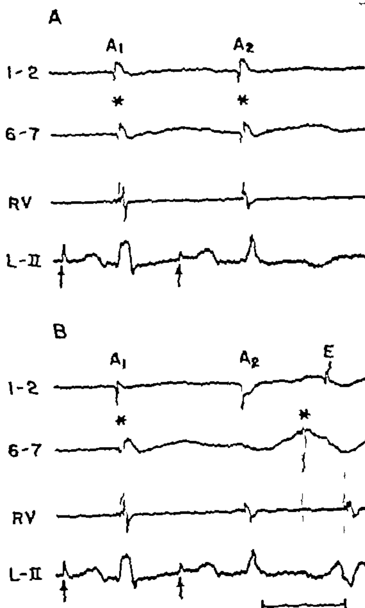



Fig. 7. Re-entrant extrasystole during cooling. Panel A shows A1 and A2 prior to cooling. Panel B shows A1 and A2 during cooling with an extrasystole. Nomenclature as in Fig. 6. Time base = 200 msec.

were dissociated by a premature impulse which took advantage of their unequal refractory periods

The results of recent experiments performed on isolated cardiac tissues also support the view that disturbances in conduction may be an important cause of ectopic rhythms Hoffman[1] and his associates have presented convincing evidence that conduction can be sufficiently slow within a small network of fibers to permit re entry The mechanism of such slow propagation appears to be decremental conduction which has been defined as a phenomenon that results when an action potential becomes progressively less effective as a depolarizing stimulus to tissues in the pathway ahead Decrement has been observed in nearly all cardiac tissues and the most frequent cause is that the action potential arises from a reduced transmembrane potential Such a reduction may occur when the entire resting potential is less than normal or it may occur if membrane potential has not fully recovered from the preceding beat or if a fully polarized membrane develops spontaneous diastolic depolarization The relevance of decremental conduction to the concept of re entry has been emphasized recently by Hoffman[13]

The experiments described in this report were designed to create a local area of nonuniform recovery and to test the response of this area to premature excitation The results suggest that this intervention produced the necessary conditions for a re entry circuit within the intact ventricle

When a focal area of the left ventricle was cooled an appropriately timed premature supraventricular beat arrived at the endocardium under the coil at a normal time but was markedly delayed on transit to the outer portions of the wall Intramural excitation was frequently delayed by as much as 90 to 1 0 msec When these conditions obtained nonstimulated ventricular extrasystoles originated from the region of the coil That the nonstimulated beats were indeed coupled to A was indicated by their absence when $A_2$ was not present

The basic cycle length was sufficiently long so that $A_1$ always propagated from endocardium to epicardium Although excitation during $A_1$ was frequently delayed in the outer wall by cooling this was not a necessary condition for the occurrence of nonstimulated beats The finding that activity persisted during $A_1$ with little or no delay indicates that muscle at all depths under the coil could be excited normally during cooling The observations that cooling caused a prolongation of the effective refractory periods under the coil and that intramural delay or block of A was a function of the $A_1$ A interval indicate that the major factor responsible for delay or block was that $A_2$ encountered refractory tissue left in the wake of $A_1$ It seems to be reasonable to postulate that the delay of $A_2$ resulted from decremental conduction in tissues with a reduced membrane potential due to incomplete recovery Intramural block may have resulted from progressive decrement or the abrupt change in refractory period at the junction between warm and cold muscle may have extinguished the propagating impulse

Bipolar tracings from the transmural electrode were obtained in such a way that negative complexes indicated outward spread of the impulse whereas positive complexes indicated inward spread During A activity at the endocardium was not delayed and the negative polarity of the complex indicated outward spread After A there was re excitation of the endocardium and the positive polarity of the complex indicated that the local spread was directed from epicardium to endocardium[14] This fact together with the observation that re-excitation of the endocardium occurred coincident with the onset of the nonstimulated beat suggest that the extrasystole originated from the intramural portion of the wall under the cooling coil Although we cannot exclude the possibility that the experimental interventions led to pacemaker centers under the coil this seems to be highly unlikely in view of the known effects of hypothermia on pacemakers Furthermore ectopic activity was never observed except when coupled to a critically timed A These data suggest therefore that the ectopic beats were passively induced by A and resulted from re-entry of the delayed

impulse at the junction between warm and cold muscle.

In panel *B* of Figs. 4, 6, and 7, the intramural leads recorded what appears to be slow electrical activity immediately after the A complex at the endocardium. These slow waves were followed after considerable delay by a sharp deflection which indicates local excitation. The mechanisms underlying these slow changes remain to be explained. We have considered the possibility that they might represent a movement artifact, but this seems to be unlikely, since the electrode was held tightly in the coil and the coil was anchored securely to the heart. It also seems to be unlikely that the slow waves represented abnormal local action potentials, since if tissue in close proximity to the contacts had depolarized coincident with A, it could not have recovered soon enough to permit a second depolarization at the times indicated by the rapid spikes. We believe that the most likely explanation for the slow wave is that a boundary existed between the fully depolarized myocardium and the focally blocked epicardial cold zone.[17] Flow of current across this boundary would be a function of the gradient in potential between the two regions. Slow waves of the type described were noted only at zones of marked delay and were not observed near the endocardium or in completely blocked epicardial regions. If the foregoing interpretation is correct, then the local nature of the slow waves and the ability to record them with a bipolar lead of 1 mm. separation imply that the boundary was relatively discrete and that the density of current created by the boundary was relatively intense.

Scherf and his associates[19] have shown previously that focal cooling of the heart can cause multiple extrasystoles, bigeminal rhythm, and ventricular fibrillation. They suggested the possibility that these arrhythmias resulted from the formation of ectopic impulses, perhaps as a consequence of a large negative after-potential. The experiments described in this report confirm the observations of Scherf and associates but suggest an alternate mechanism based on re-entry.

The observations of Scherf, as well as those reported in this paper, would appear to have a bearing on the nature of arrhythmias during clinical hypothermia. Perfusion hypothermia is usually associated with intramyocardial temperature gradients[19] and the incidence of ventricular arrhythmias can be reduced by techniques which reduce the magnitude of these gradients.[4] Nonuniform cooling of the heart would be expected to have nonuniform effects on recovery of excitability. If phenomena of the type described in this report occur at junctional zones between areas of differing temperature, then the possibilities by which such a nonhomogeneous system might respond in a disorganized manner are numerous.

In addition to temperature gradients, a large number of other arrhythmic influences, including ouabain, ischemia, sympathetic nerve stimulation, and overdoses of quinidine, enhance the degree of nonuniformity of the ventricle. These influences also increase the likelihood of multiple responses or fibrillation after primary excitation.[8,20] Although it has been assumed that fractionation of an impulse and re-entry might occur, direct evidence that nonuniform recovery actually produces the conditions necessary for re-entry in the intact ventricle has not been described previously. The experimental observations reported above provide support for the view that nonuniform recovery of excitability can be a factor of major importance in enhancing the propensity of a heart to the formation of extrasystoles and to fibrillation.

Finally, we believe that it is of interest that many features of the local sequence under the cooling coil resemble functional characteristics normally ascribed to the A-V node. Delay between endocardium and epicardium might be considered to be analogous to first-degree A-V block, intermittent patterns to be similar to second-degree block, and complete failure of $A_1$ to reach the epicardium to be analogous to third-degree block. The conditions under which A produced nonstimulated extrasystoles are similar to those characterizing echo responses which originate from the A-V node. The possibility that the junction between areas of differing excitability might demonstrate behavior similar to that of the A-V node, including

re entry provides a conceptual model which could account for many clinically encountered disturbances in cardiac rhythm


## Summary

These experiments were designed to test the re entry hypothesis as a mechanism for the formation of extrasystoles Studies were performed on 10 dogs with the heart exposed Pacing wires were attached to the right atrium and connected to a set of pulse generators The heart was paced at a basic frequency and a premature atrial stimulus was delivered after each sixth basic beat A small silver coil was used to vary the temperature of a focal area of left ventricle and a multipolar electrode was advanced through the coil and used to record local depolarization

When ice water was perfused through the coil temperatures in the outer portion of the ventricular wall were reduced Cooling lengthened the effective refractory period under the coil and produced a marked increase in the temporal dispersion of recovery between endocardium and epicardium When sufficiently premature stimuli were applied to the atrium the ventricular response reached the endocardium normally but encountered refractory muscle under the coil on transit to the epicardium At the junction between warm and cold muscle propagation of the early response was markedly delayed and finally blocked near the epicardium When the local delay was sufficiently great nonstimulated ventricular extrasystoles appeared which were coupled to the preceding beat The nonstimulated extrasystoles originated from the region of the coil and were initiated by activity which was directed from epicardium to endocardium On several occasions a nonstimulated beat was followed by multiple ventricular extrasystoles and by ventricular fibrillation

These observations indicate that cooling of a discrete area of the left ventricle created the necessary conditions for re entry and that extrasystoles resulting from re-entry were produced These data also emphasize the potentially arrhythmic consequences of any influence which enhances nonuniform recovery in the heart and suggest that the junction between areas of different refractory periods within the ventricle can demonstrate behavior similar to that of the normal A V node



The technical help of Mr James Manley Miss Eleanor Timmerman and Mr William Joyner was of great assistance in these studies



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# The selective uptake of $Hg^{203}$-chlormerodrin in experimentally produced myocardial infarcts

*Ralph J. Gorten, M.D.***
*Lawrence B. Hardy, B.A.****
*Burley H. McCraw, M.A.*****
*John R. Stokes, F.I.M.L.T.****
*George D. Lumb, M.D., M.R.C.P.*******
*Durham, N.C.*

The detection of myocardial infarcts in animals and human subjects by a photoscanning technique has been reported recently by Carr and associates[1] and by Evans and associates. With further developments the procedure holds promise of providing information in regard not only to the location but also to the extent and severity of myocardial damage. The following studies of experimental coronary arterial occlusion were designed to investigate the selective localization of certain radioactive chemicals in areas of myocardial damage and to correlate information gained by photoscanning with gross radiologic and histologic examination of the tissues.

## Methods

Gradual occlusion of the left circumflex artery was produced in a series of animals by surgical application of a sterile hygroscopic casein base plastic (Ameroid) constrictor (1.57 mm. in diameter) 5 mm. from the ostium of this artery. As previously described, these constrictors close completely in 48 hours when placed in saline at 37 C.[3] Therefore occlusion of the arteries was considered to be complete in all animals by 60 hours.

Because the distribution of coronary arteries in swine is similar in many respects to that in man,[4] mongrel pigs were selected for these experiments. A total of 76 animals with a weight range of 11 to 27 kilograms was used. Two animals were excluded because of pulmonary disease discovered at the time of operation, and 1 was excluded for failure to recover from the anesthetic. Forty animals (55 per cent) died and represent the mortality figures for gradual occlusion of the left circumflex

From the Radioisotope and Medical Services, Veterans Administration Hospital, and the Department of Medicine, Duke University Medical Center, Durham, N.C., and the Department of Pathology, [illegible] Memorial Hospital, [illegible], N.C.
Presented in part at the 37th Scientific Sessions of the American Heart Association, Oct. 23, 1964.
Supported in part by Grant [illegible] from the National Institutes of Health, United States Public Health Service (Dr. Lumb), and grants from the North Carolina Heart Association and [illegible] Laboratories.
Received for publication Oct. 13, 1965.
*Assistant Professor of Medicine and Associate in Physiology, Duke University School of Medicine, and Chief, Radioisotope Service, Veterans Administration Hospital, Durham, N.C.
**Formerly Department of Pathology, [illegible] Memorial Hospital; Present address: Warner-Lambert Research Institute, Morris Plains, N.J.
***Formerly Radioisotope Service, Veterans Administration Hospital, Durham, N.C.
****Formerly Director, Department of Pathology, [illegible] Memorial Hospital, and Associate Professor of Pathology, University of North Carolina School of Medicine, Chapel Hill, N.C.




Fig. 1 Heart placed in the two positions used for photoscanning. A, Closed with anterior surface up (operative site in upper center). B, Cut and unrolled with the endocardium facing detector.

artery by this technique. Thirty seven died in the first 3 days and the other 3 by the end of the fifth day.

The 33 pigs which survived the effects of arterial occlusion were divided into 3 groups in order to study myocardial infarcts at different time intervals after occlusion. Animals in Group I were sacrificed 3 to 5 days after surgical application of the constrictors; the intervals were 6 to 8 days for Group II and 9 to 12 days for Group III.

Twelve to 14 hours prior to scheduled sacrifice 1.6 millicuries of Hg 203 chlormerodrin (Neohydrin*) were administered into the external jugular vein of each pig. At autopsy each heart was examined for gross evidence of myocardial damage and the presence of other lesions was excluded. The excised hearts were washed free of blood. Photoscanning was performed with the anterior surface of the intact heart toward the detector (Fig. 1 A). The hearts were then cut and unrolled [3] and the photoscan was repeated with the endocardial surface toward the detector (Fig. 1 B). A radioisotope photoscanning system† with a 5 inch diameter scintillation detector and a focusing collimator of 61 holes with a focal length of 3¼ inches was used at 19 inches per minute. The pulse height analyzer window was 40 Kev wide. No background cutoff was used. Brightness contrast and scale factor controls were set according to the maximum counts per minute in each heart (600 to 9,000 counts per minute). The primary aim was to obtain the greatest degree of contrast between areas of higher and of lower rates. Areas of higher count rates indicating a selective uptake of the radioactive tracer were read on the photoscans and graded 3, 2, 1, or 0 according to the degree of contrast between the dark (or "hot") area and the rest of the myocardium.

Anatomic and histologic examinations were performed on all hearts and areas of infarction were described.

Nine hearts selected at random were perfused through the right coronary artery with a barium sulfate suspension (Micropaque*) at physiologic pressures.[4] Roentgenograms of the closed and unrolled hearts demonstrated the distribution of the right coronary artery together with any collateral passage into the left coronary system. Comparative studies of the infarcted areas were made using these radiographs, the photoscans, and outline drawings of the naked eye appearances of the gross specimens.

*E. R. Squibb and Sons Radiopharmaceutical Department, New Brunswick, N. J., and Abbott Laboratories Radiopharmaceutical Department, Oak Ridge, Tenn.
†Nuclear-Chicago Inc., Cleveland, Ohio, and Picker Instrument Company, Downers Grove, Ill.

*Micropaque powder, Damancy & Co. Ltd., Ware, Herts, England. Supplied in U.S.A. by Picker X-Ray Corp., White Plains, N. Y.

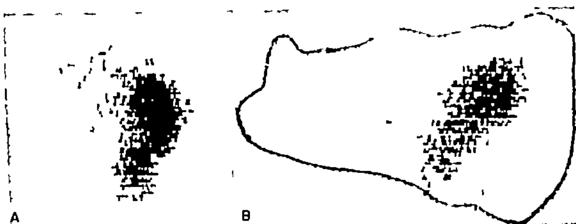



Fig. 2. *A* and *B*. Example of photoscans showing greatest degree of contrast between area of infarction and rest of myocardium (Grade 3). Shape of closed heart in *A* can be detected by slightly greater than background count of radioactivity in normal myocardium. Differences in count rate were too small in "unrolled" heart (*B*). Therefore, perimeter of specimen was drawn in for better orientation.




Fig. 3. *A* and *B*. Photoscans showing easily detectable area of increased radioactivity but less in degree of contrast than heart depicted in Fig. 2 (Grade 2).

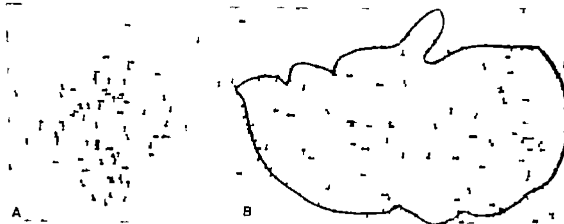



Fig. 4. *A* and *B*. Photoscans showing [illegible] (Grade 0).

**Results**

Of the 33 hearts examined by photoscanning, 26 (79 per cent) demonstrated areas of increased radioactivity. These were in the posterolateral wall of the left ventricle at the site expected for infarction from occlusion of the left circumflex artery. Scans of hearts from 5 sham-operated animals and from 3 animals on which no operations were performed showed no localization of the tracer.

There was considerable variation in the degree of selective uptake of the radioactive material in the positive heart scans. These differences were graded by four independent observers by visual inspection according to the degree of contrast between a hot area and the rest of the heart. The grading of all scans was repeated on four occasions in order to avoid changes in standards of classification during the course of the study.

A scan demonstrating the greatest degree of contrast (Grade 3) is shown in Fig. 2. In Fig. 3 the hot area in the left ventricular myocardium is also easily detected but the contrast is less in degree (Grade 2). Scans without any area of selective uptake were given Grade 0 (Fig. 4). Grade 1 was assigned to scans with barely detectable or equivocal areas of increased uptake.

An inverse relationship between the age of an infarct and the degree of selective uptake of $Hg^{203}$ by the area of ischemic muscle is suggested by scan data as summarized in Table I. All scans classified Grade 3 (those demonstrating the most obvious dark areas) were in Group I, the animals sacrificed 3 to 5 days after application of the plastic constrictors. All but one of the scans lacking any selective localization (Grade 0) were from the hearts of animals in Groups II and III.

Areas of infarction identified by gross and microscopic examination showed excellent correlation with the results of photoscanning. The anatomic site and overall size, where it could be measured, corresponded closely with the areas of selective localization of the radioactive tracer. Gross evidence of infarction was seen in all hearts of Group II. In one heart of Group I no gross abnormalities could be detected, probably because the changes were in a very early stage. In Group III gross changes were obvious in all but 3 hearts. In these healing had progressed sufficiently to make the identification of infarcts no longer possible.

Histologic evidence of myocardial damage was demonstrated in all hearts. This varied from cellular fragmentation and irregular staining reactions in Group I to evidence of healing with fibroblastic activity in areas of myocardial necrosis in Group III. The hearts in Group II showed typical infarction with myocardial fiber necrosis and inflammatory infiltration.

Equivocal evidence of myocardial damage could be demonstrated by routine histologic methods in one heart of Group I. It is of interest that this was the only heart in this group which gave a negative photoscan. The other scans in animals of Group I, the group in which total arterial occlusion had been present only 3 to 5 days and in which histologic changes were early but definite, showed a high degree of contrast. In Group III, where fibroblastic activity indicated healing and active myocardial fiber degeneration was minimal, the photoscans showed a low degree or absence of localized radioactivity.

The radiographs of 9 hearts which were perfused with Micropaque showed areas of radiotranslucency surrounded by fluffy radiopaque areas which appeared to be

*Table I. Distribution of scan grades according to age of infarct*

| Group | Days | Number | Scan grade | | | |
|---|---|---|---|---|---|---|
| | | | 3 | 2 | 1 | 0 |
| I | 3-5 | 13 | 5 | 5 | 2 | 1 |
| II | 6-8 | 10 | 0 | 2 | 6 | 2 |
| III | 9-12 | 10 | 0 | 0 | 6 | 4 |
| | | 33 | | | | |

Grade 3 denotes the greatest degree of [illegible] Grade 2 [illegible] Grade 1 was assigned to scans [illegible] equivocal areas of increased uptake. Grade 0 [illegible] absence of selective uptake on the scan.



Fig 5 Radiograph of unrolled heart showing area of translucency in posterolateral wall of left ventricle surrounded by fluffy zone Perfusion with Micropaque was through the right coronary artery only Constrictor can be seen on the left circumflex artery



Fig 6 Photoscan of heart seen in Fig 5 shows area of increased radioactivity in same location as radiotranslucen

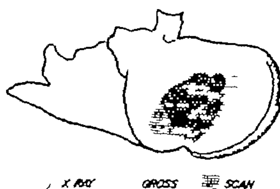



Fig 7 Outline drawing of same unrolled heart as in Figs 5 and 6 depicting position of infarct as seen by (a) naked eye (b) photoscan hot area and (c) translucent and fluffy zone in radiograph

small vessels (Fig 5) These zones were in the posterolateral wall of the left ventricle and corresponded to the infarcts visible on gross examination and the hot areas detected by the photoscans (Figs 5 6 and 7) Because the left circumflex artery was occluded in all cases and the radio paque material was introduced only through the right coronary artery the filling of the anterior descending and all other branches of the left coronary artery resulted from retrograde flow presumably through collateral vessels

Certain factors other than age of the infarct and extent of myocardial damage may have influenced the results of the scanning To determine whether radio activity was contained mainly in vessels congested with stagnant blood the coronary vessels of 4 scanned hearts were thoroughly flushed with physiologic saline solution and the scans were repeated Differences which were only barely noticeable could be detected in the prints of respective scans The areas of greatest radio activity were not appreciably altered (Fig 8)

In 4 hearts microscopic evidence of slight but definite pericarditis was observed However 3 of the 4 hearts had been given scan grades of 0 to 1 This suggested that the role of inflammatory reaction involving the pericardium as a result of the operative procedure or concomitant with the myocardial infarct had little influence on the photoscan Two hearts which revealed hemorrhagic spots on gross examination had scan grades which varied from 0 to 3 None demonstrated hot areas localized to the sites of hemorrhage

It was concluded therefore that the areas of selective localization of radio activity were caused by myocardial damage produced as a result of the experimental gradual narrowing to occlusion of the left circumflex artery and not as a result of overlying pericarditis or vascular congestion or hemorrhage

**Discussion**

Radioisotope photoscanning depicts the spatial distribution of a radioactive chemical substance in an organ Potentially this procedure can aid in the evaluation of myocardial infarcts in patients and of experimentally produced infarcts in animals by providing objective information in addition to the electrocardiograms enzyme levels and morphologic changes Substances such as cesium 131 or iodinated ($I^{131}$) oleic acid materials taken up by normal myocardium can be used to depict infarcts as cold areas on heart scans[1,5]

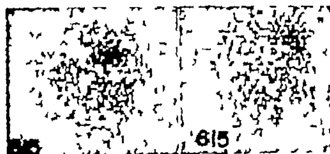



Fig 8 Photoscans before (left) and after (right) coronary vessels were flushed with saline

To define areas of muscle damage in the excised hearts of laboratory animals with experimentally produced arterial occlusion, it is advantageous to use $Hg^{203}$ chlormerodrin (Neohydrin) which is localized selectively in damaged myocardium. Such areas show up as dark or hot regions in comparison to the healthy myocardium. This material has been used to detect myocardial infarcts in living animals.[7] Carr and associates,[1] who limited the tracer dose to 700 microcuries, reported poor success in a series of patients with clinically diagnosed infarcts. Probably in all periods greater than 3 days had elapsed before the scans were performed.

Studies in living subjects are hindered considerably by the movements of the heart, the presence of radioactive indicator in the blood within the heart and in the lungs, and the scattering by the tissues of the thoracic wall. It must be realized that in this study a larger tracer dose and scanning of excised, washed animal hearts provided more optimum conditions for precise definition of the areas of necrosis.

The results of this study indicate that the radioactive tracer is able to reach portions of myocardium in which the main supply of blood is occluded and in which fiber degeneration is taking place. There is excellent correlation between hot areas on scans and zones of myocardial damage, whether patchy or diffuse. Fibroblastic tissue in necrotic areas does not take up the radioactive material. Variation in the degree of uptake of the radioactive chemical in the hearts studied was caused mainly by differences in time after arterial occlusion and by differences in concentration and size of foci of necrosis in ischemic myocardium. The mechanism of selective localization in areas of myocardial fiber degeneration is still open to speculation. It is very unlikely that this is caused by vascular congestion, hemorrhage or overlying pericarditis. It may be that in areas of severely reduced blood supply capillary permeability is altered sufficiently to allow significant amounts of Hg labeled chlormerodrin to escape into the interstitial fluid so that it (or the mercury alone) can be bound by the sulfhydril groups of the cell proteins.

Changes in staining properties of myocardium are difficult to interpret by light microscopy in the period immediately after arterial occlusion, and infarcts are not recognized with certainty within the first 2 days. Also it is difficult to estimate the size of infarcts by routine morphologic methods.[6] On the other hand, distinct localization by radioisotope scanning was demonstrated frequently in hearts with infarcts showing only early cellular damage. Selective uptake of $Hg^{203}$ was demonstrated in 12 of the 13 hearts in Group I. This indicates that this technique is of greatest usefulness in the identification of myocardial damage in the first 7 to 8 days after coronary occlusion.

**Summary**

Infarcts of the posterolateral wall of the left ventricle were produced in 73 swine by gradual occlusion of the left circumflex artery. $Hg^{203}$ chlormerodrin was injected intravenously into 33 survivors 12 to 14 hours before sacrifice.

Photoscanning of intact and unrolled hearts showed a hot area of selective uptake of the isotope in the area of the infarct which correlated well in location and extent with pathologic observations. Intensity of selective uptake varied inversely with the length of time after application of the constrictor.

Photoscanning of selective uptake of $Hg^{203}$ chlormerodrin is a valuable method for demonstrating areas of myocardial infarcts before replacement by fibroblastic tissue.

We are very grateful to Drs. Eugene A. Stead, Jr., E. Harvey Estes, J. Kaye, H. Kilburn, Felix J. Pircher, and Aaron P. Sanders for helpful suggestions and critical review of the manuscript. Messrs. L. Hart, J. E. [illegible] and D. Powell skillfully prepared the illustrations.

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# Experimental revascularization of the entire heart

## Evaluation of epicardiectomy, omental graft, and/or implantation of the internal mammary artery in preventing myocardial necrosis and death of the animal

*Arthur M. Vineberg, M.D.**
*Yutaka Kato, M.D.*
*W. J. Pirozynski, M.D.*
*Montreal, Canada*

The value of surgical techniques for the relief of coronary artery insufficiency has been greatly doubted. This has been partly because clinical evaluation of revascularization procedures is difficult due to the unpredictable character of the disease and partly because basic experimental methods of evaluation of an operative procedure have been lacking.

Many studies in our laboratory have made it quite clear that evaluation of a revascularization procedure by flow, backflow, ventricular fibrillation threshold, radioactive tracings, and many other such methods left a great deal to be desired and for the most part could not be relied upon. For this reason, over the years we have attempted to reproduce coronary artery occlusion by constricting the main stems at the locations at which obstructive disease occurs in human patients.[1-9]

Experiments have been carried out until a 100 per cent lethal test has been developed as a result of slow occlusion of the main stems of all three coronary arteries by Ameroid constrictor.[10]

Besides survival of the animal from triple coronary artery occlusion, the degree of myocardial necrosis in both ventricles has been used as objective evidence of the value of a revascularization procedure. In addition, intra-arterial injection studies using Schlesinger mass[11] have been carried out in order to outline the extracardiac coronary pathways which may or may not develop and which, when present, might explain any benefit that occurred as a result of a given revascularization procedure.

### Experimental study

Various methods of revascularization were tested against the 100 per cent coronary artery Ameroid occlusion test.

*A. Control group.* In the control series of 20 animals there were 20 deaths; the spontaneous mortality was 100 per cent. The average survival time was 18.8 days; this was used as a base line to estimate the survival time. Survival time, therefore, becomes one of the criteria for the evaluation of various surgical procedures de-

From the Sub-Department of Cardiac Surgery, Royal Victoria Hospital, and the Department of Experimental Surgery and Pathology, McGill University, Montreal, Canada.

Received for publication Oct. 22, 1965.

*Address: Sub-Department of Cardiac Surgery, Royal Victoria Hospital, Montreal, Quebec, Canada.

signed to relieve myocardial ischemia caused by triple coronary artery constriction.

*B. Treated groups.* In all animals the Ameroid coronary artery constrictors were applied at the time of one of the following operative procedures:

1. EPICARDIECTOMY—10 ANIMALS. The epicardium was removed from the anterolateral and posterior surfaces of both ventricles using specially designed epicardial scrapers which remove both layers of the epicardium without injury to the coronary vessels.

2. EPICARDIECTOMY AND SEROUS PERICARDIECTOMY—10 ANIMALS. The epicardium and serous layer of the pericardium were removed and the pericardium was closed.

3. EPICARDIECTOMY WITH INTERNAL MAMMARY ARTERY IMPLANTATION (VINEBERG)—10 ANIMALS. The left internal mammary artery was implanted into the anterior wall of the left ventricle. The epicardium was removed from the remainder of the left ventricle. The pericardium was left open.

4. FREE OMENTAL GRAFT OPERATION (VINEBERG)—10 ANIMALS. The entire heart was wrapped around by a graft of the greater omentum which was completely detached from its abdominal pedicle and the diaphragm was closed. The omentum was not sutured to the heart but to the ascending aorta. Epicardiectomy and serous pericardiectomy were not performed. The pericardium was closed over the omental graft.

5. FREE OMENTAL GRAFT OPERATION PLUS EPICARDIECTOMY AND SERO-PERICARDIECTOMY (VINEBERG)—20 ANIMALS. Extensive epicardiectomy of all surfaces of both ventricles was performed, the serous layer of the pericardium was removed, as was the reflection of the pericardium over the base of the aorta. The greater omentum, after its detachment from the transverse colon, was wrapped around the heart. It was fixed by multiple sutures to the ascending aorta and the heart. The pericardium was closed.

6. FREE OMENTAL GRAFT PLUS EPICARDIECTOMY AND SERO-PERICARDIECTOMY WITH INTERNAL MAMMARY ARTERY IMPLANTATION OPERATION (VINEBERG)—14 ANIMALS. The same technique as described under 2, 3, and 5 was followed. The left internal mammary artery was implanted into the anterior wall of the left ventricle. The pericardium was resected anteriorly to prevent encroachment upon the internal mammary artery implant. The omental graft was sutured to the free edges of the pericardium and to the anterior surface of the heart to avoid contact with the internal mammary artery.

**Postmortem studies**

All animals underwent the following investigations:

*A. Injection studies.* The chest was opened through the fourth intercostal space; adhesions to the surface of the heart were not disturbed.

The aorta was ligated above the diaphragm and at its junction with the left ventricle. Care was taken not to damage anastomotic vessels between the aorta and the omental graft. The thoracic aorta was cannulated proximal to the lower ligature. New Schlesinger mass, which does not pass through vessels that are less than 40 microns in diameter, was injected at pressures that ranged between 100 and 120 mm. of mercury, filling the aorta and its branches above the diaphragm with dye. Reflux of injection mass into the left ventricular cavity and coronary arteries was prevented by the ligature at the aortoventricular junction. Thus radiopaque substances appearing in the coronary arteries could only have entered them by traversing extracardiac coronary anastomoses via the subpleural mediastinal and pericardial vessels. X-ray films of the heart in situ before and after injection outlined the extracardiac coronary anastomoses when present.

In the group of animals which had undergone the combined free omental graft and internal mammary artery implantation operation, the internal mammary artery was ligated at the second intercostal space and cannulated distal to the ligature. The radiopaque mass injected into the thoracic aorta filled mediastinal vessels and outlined omental-coronary anastomoses as well as omental and/or mammary-coronary anastomoses. After injection and x-ray examination in situ, the internal

mammary artery was injected under systemic pressure and the heart was x-rayed again in situ.

After removal of the heart, the ascending aorta was reinjected with Schlesinger mass so as to fill vessels leaving the root of the aorta to anastomose with those in the omental graft. The ligature around the base of the aorta was not removed.

When the original aortic injection did not fill the entire coronary arterial tree, then both coronary ostia were cannulated with metal cannulae and injected with Schlesinger mass. Separate x-ray films were taken after injection of each coronary artery.

After the injection mass had solidified, the heart was unrolled in order to study homocoronary and intercoronary anastomoses as well as arterial channels which were formed to bypass the areas of Ameroid obstruction of the coronary arteries.

Multiple x-ray pictures taken between the injections of radiopaque Schlesinger mass have made it possible to outline numerous arteriolar and larger vessels and to study anastomoses formed between (a) the aorta and free omental graft, (b) the graft-coronary arteries and myocardium, (c) mediastinal vessels-pericardium-graft and coronary myocardial vessels, and (d) internal mammary artery-myocardial arterioles and coronary arterioles.

Injection studies are not so definitive as survival of animals and ventricular muscle mass. However, newly developed extracardiac channels through which oxygenated blood can bypass the proximal points of coronary artery occlusion may be outlined. In this study, the injection mass was first introduced into the thoracic aorta in order to outline extracardiac coronary anastomoses. The filling of the coronary arterial tree through the aorta via mediastinal vessels may prevent satisfactory visualization of homocoronary and intercoronary anastomoses by later individual coronary artery injections. This occurs because the injection mass hardens before there is time to remove the heart and inject the coronary arteries. Thus the first injection should outline the important channels immediately. In this series, our attention has been focused upon the extracardiac channels reaching the heart from the mediastinal vessels. The demonstration of homocoronary and intercoronary arteries, although desirable, was regarded to be of secondary importance. In most instances these have also been outlined satisfactorily.

*B. Pathologic studies.* Each heart was examined grossly and microscopically for presence or absence and extent of ischemic myocardial damage. Multiple sections were taken from the right and left ventricles and the intraventricular septum.

The portions of each artery included in the Ameroid constrictors were investigated microscopically to determine the extent of narrowing of the lumina of the right anterior descending and circumflex coronary arteries. This has been recorded as the percentage occlusion of the original cross-sectional area of the lumen. It has been expressed as an average occlusion for all three coronary arteries.

The patency of the implanted internal mammary artery was determined over its entire length, including the myocardial tunnel.

**Results**

In this study we have attempted to establish simple criteria for estimating the value of a revascularization procedure. The four most important criteria of value are: (1) survival time of animals, (2) extent of damage to the myocardium after triple coronary artery Ameroid constriction, (3) formation of extracardiac coronary anastomotic channels, and (4) formation of a new surface cardiac distribution system (omental graft) connecting together right and left coronary systems and arteriolar zones.

*1. Survival of animals.* The survival times of both the control series and the treated series are shown in Table I.

CONTROL GROUP. In the control series the spontaneous mortality was 100 per cent.

TREATED GROUPS.

1. In the series of 10 animals with epicardiectomy there was one death, i.e., 90 per cent spontaneous mortality. The average survival was 16 days; there was one long-term survivor sacrificed 266 days postoperatively.

2. In the second series of 10 animals in which the epicardium and serous layer of

*Table I. Survival time after triple coronary artery Ameroid constriction (control and treated)*

| | Number of animals in series | Died: Number of animals | Died: Average number of days | Died: Range in days | Died: Spontaneous mortality (%) | Sacrificed: 235-440 days (%) | Sacrificed: Average number of postop. days |
|---|---|---|---|---|---|---|---|
| Control | 20 | 20 | 19 | (9-2?) | 100 | | |
| Treated | | | | | | | |
| 1. Epicardiectomy | 10 | 9 | 16 | (7-28) | 90 | 1-10 | 266 |
| 2. Epicardiectomy and sero-pericardiectomy | 10 | 8 | 30 | (21-40) | 80 | 2-20 | 245 |
| 3. Epicardiectomy and internal mammary artery implant | 10 | 6 | 24 | (15-39) | 60 | 4-40 | ?5 |
| 4. Free omental graft | 10 | 6 | 20 | (9-30) | 60 | 4-40 | 235 |
| 5. Epicardiectomy, sero-pericardiectomy, and free omental graft | 20 | 5 | 26 | (17-37) | 25 | 15-75 | 322 |
| 6. Epicardiectomy, sero-pericardiectomy, free omental graft, and internal mammary artery implant | 14 | 3 | 32 | (19-50) | 21 | 11-79 | 294 |
| Total | 94 | | | | | 3? | |

[illegible] of coronary [illegible] Died [illegible] 71.3 [illegible] 76.2 per cent [illegible] 82.3 [illegible]

the pericardium were removed, there were 8 deaths, a spontaneous mortality of 80 per cent. Survival time averaged 30 days. Two long-term survivors were sacrificed after 245 days postoperatively.

3. In the third group of 10 animals with epicardiectomy and internal mammary artery implantation there were 6 deaths, the spontaneous mortality was 60 per cent. The average length of survival was 24 days. There were 4 (40 per cent) long-term survivors studied approximately 75 days postoperatively.

4. In the fourth series of 10 animals in which the free omental graft was wrapped around the heart there were 6 deaths, a spontaneous mortality of 60 per cent. The average length of survival was 20 days. There were 4 long-term survivors (40 per cent) studied on an average of 235 days postoperatively.

5. In the fifth series of 20 animals in which the epicardiectomy, sero-pericardiectomy, and free omental graft operations were performed there were 5 deaths, a spontaneous mortality of 25 per cent. The average survival was 26 days. There were 15 long-term survivors (75 per cent); these were sacrificed and studied on an average of 322 days postoperatively.

6. In the final series of 14 animals which underwent epicardiectomy, sero-pericardiectomy, free omental graft application and internal mammary artery implantation there were 3 deaths, a spontaneous mortality of 21 per cent. The average survival was 32 days. There were 11 long-term survivors (79 per cent); these were sacrificed for study on an average of 294 days postoperatively.

*Pathologic studies.* The pathologic findings of the control animals and those

*Table II Tabulation of myocardial damage in experimental animals after triple Ameroid coronary artery constriction*

| | Number of animals in series | Animals dying spontaneously | | | | | Animals sacrificed | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Number of animals | Myocardial damage | | | | Number of surviving animals | Myocardial damage | | | |
| | | | None | Focal | Moderate | Massive | | None | Focal | Moderate | Massive |
| Control | 20 | 20 | 0 | 1 | 2 | 17 | | | | | |
| Treated | | | | | | | | | | | |
| 1 Epicardiectomy | 10 | 9 | 0 | 0 | 4 | 5 | 1 | 0 | 1 | 0 | 0 |
| 2 Epicardiectomy and sero-pericardiectomy | 10 | 8 | 0 | 6 | 2 | 0 | 2 | 0 | 2 | 0 | 0 |
| 3 Epicardiectomy and internal mammary artery implant | 10 | 6 | 0 | 4 | 2 | 0 | 4 | 0 | 4 | 0 | 0 |
| 4 Free omental graft | 10 | 6 | 0 | 0 | 1 | 5 | 4 | 0 | 3 | 1 | 0 |
| 5 Epicardiectomy, sero-pericardiectomy and free omental graft | 20 | 5 | 0 | 2 | 2 | 1 | 15 | 5 | 10 | 0 | 0 |
| 6 Epicardiectomy, sero-pericardiectomy, free omental graft and internal mammary artery implant | 14 | 3 | 0 | 2 | 0 | 1 | 11 | 7 | 4 | 0 | 0 |

which have been subjected to various surgical procedures are summarized in Tables II and III. A differentiation has been made between those animals which died from myocardial ischemia and those which were sacrificed many months after surgery.

For those animals which died spontaneously the average degree of coronary artery occlusion ranged from 71.3 to 76.2 per cent in all groups. In those animals which were sacrificed up to 469 days after surgery there appeared to be an increase in the degree of coronary artery occlusion as time went on and the average degree of cross-sectional occlusion of the total coronary artery inflow tract ranged from 82.3 to 86.? per cent for the survivors in all six treated groups (Fig. 1).

The extent of myocardial damage was graded as follows: No myocardial changes 0. Focal infarcts (not grossly visible) +. Moderate or large infarcts—(grossly noticeable—confined to one surface) ++. Massive—transmural infarcts (gross and microscopic) +++.

The animals were grouped according to the operative procedure and to the mode of death (i.e. spontaneous or sacrificed). In the control group 95 per cent of all animals showed massive to moderate myocardial damage in one or both ventricles at the time of spontaneous death.

Epicardiectomy alone appears to have little beneficial effect on the prevention of massive myocardial infarction in either right or left ventricles in those animals which died spontaneously.

In the second group in which epicardiectomy was combined with serous pericardiectomy no massive infarction was present in the animals.

In the third group the implanted internal

Table III Pathologic study

**Triple coronary artery occlusion**

| Dog No | Survival days | Right ventricle: Ant | Right ventricle: Lat | Right ventricle: Post | Left ventricle: Ant | Left ventricle: Lat | Left ventricle: Post |
|---|---|---|---|---|---|---|---|
| 591 | 9 | | | | +++ | | |
| 99 | 11 | | | | +++ | | |
| 165 | 11 | | | +++ | | | +++ |
| 778 | 13 | | | | +++ | | |
| 324 | 14 | | + | +++ | +++ | | +++ |
| 124 | 17 | | | | + | | |
| 769 | 18 | | | | +++ | | |
| 734 | 18 | | + | | +++ | | + |
| 325 | 18 | | + | +++ | | | +++ |
| 132 | 19 | +++ | | | | | |
| 708 | 19 | +++ | +++ | +++ | +++ | | |
| 16 | 20 | | | | +++ | | |
| 621 | 0 | | | +++ | | | +++ |
| 327 | 20 | | ++ | | | | |
| 79 | 25 | | | | +++ | +++ | +++ |
| 551 | 23 | +++ | +++ | | | | |
| 418 | 23 | +++ | +++ | +++ | | | |
| 136 | 25 | | | | | | Apex ++ |
| 115 | 26 | | | | +++ | | |
| 104 | 2? | | | | +++ | | |

**Free omental graft, epicardiectomy, and pericardiectomy**

| Dog No | Survival days | Right ventricle: Ant | Right ventricle: Lat | Right ventricle: Post | Left ventricle: Ant | Left ventricle: Lat | Left ventricle: Post |
|---|---|---|---|---|---|---|---|
| 335 | 17 | | | +++ | | | +++ |
| 910 | 73 | | | | ++ | | |
| 645 | 26 | + | + | | ++ | | |
| 971 | 26 | | + | | + | | |
| 113 | 37 | | | + | | | + |
| 818 | 189 | | | | | | Sept + |
| 437 | 215 | | | + | | | + |
| 760 | 229 | | | | + | + | |
| 57 | 30 | | | | | | + |
| 455 | 232 | | | | | | |
| 854 | 253 | | | | | | |
| 603 | 279 | | + | | + | | |
| 916 | 287 | | | | + | + | |
| 70 | 303 | + | + | | + | | |
| 531 | 310 | | | | | | |
| 199 | 460 | | | | + | | |
| 46 | 46 | | | | | | |
| 482 | 468 | | | + | | | + |
| 90* | 469 | | | | | | |
| 137 | 469 | | | | | + | + |

**Internal mammary artery implantation, epicardiectomy, free omental graft**

| Dog No | Survival days | Right ventricle: Ant | Right ventricle: Lat | Right ventricle: Post | Left ventricle: Ant | Left ventricle: Lat | Left ventricle: Post |
|---|---|---|---|---|---|---|---|
| 922 | 19 | + | | +++ | | | +++ |
| 546 | 75 | | | | + | | + |
| 44 | 50 | | | | + | | |
| 874 | 105 | | | | | | |
| 534 | 223 | | | | | | |
| 557 | 234 | | | + | + | + | |
| 835 | 35 | | | | | | Sept + |
| 575 | 156 | | | + | | | + |
| 641 | 309 | | | | | | |
| 99 | 331 | | | | | | |
| 949 | 360 | | | | | | |
| 889 | 362 | + | + | | | | |
| 555 | 418 | | | | | | |
| 681 | 423 | | | | | | |

*Survived
+ Focal infarcts ++ Moderate or large infarct +++ Massive—transmural infarcts

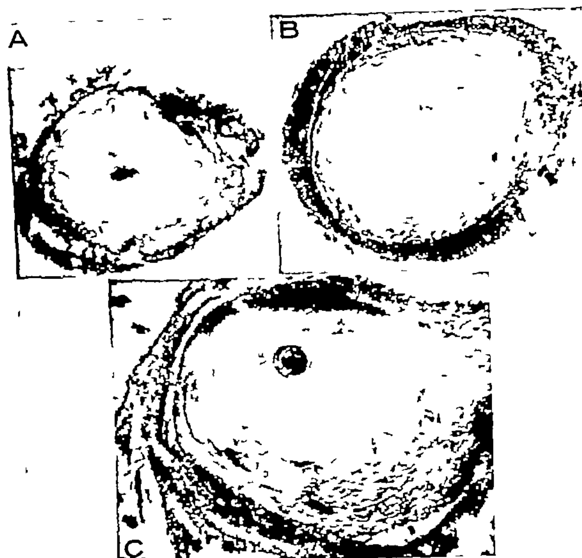



Fig. 1. Photomicrograph of sections taken from the sites of Ameroid placement on coronary arteries in Animal No. 157 which was sacrificed 469 days postoperatively. A, Photomicrograph section through the right coronary artery within the Ameroid; the degree of obstruction was 94.1 per cent. *B*, Photomicrograph of section taken through the anterior descending branch within the Ameroid; the degree of obstruction was 78.5 per cent. *C*, Photomicrograph of section taken through the circumflex coronary artery at the site of Ameroid constriction showing 90 per cent occlusion of the lumen. The average degree of cross-sectional occlusion of the total coronary artery inflow tract in those animals that were sacrificed ranged from 8[illegible].3 to 86 per cent.

mammary artery combined with epicardiectomy prevented massive myocardial infarction in all animals.

The simple omental graft without pedicle operation protected 40 per cent of the animals from massive myocardial infarction.

When epicardiectomy, sero-pericardiectomy and omental graft were performed, 5 (25 per cent) had no infarction and 10 (50 per cent) had scattered foci of fibrosis; none of the 75 per cent survivors had moderate to massive infarction.

In the last series in which epicardiectomy, sero-pericardiectomy, omental graft and internal mammary artery implant were performed, 11 of 14 animals survived. 7 of these (50 per cent) showed no myocardial infarction in either ventricle and 4 (36 per cent) showed only scattered

foci of fibrosis None of the 11 surviving animals showed any evidence of moderately severe or massive myocardial infarction All implants were patent The average internal mammary artery patency for surviving animals was 71 8 per cent

In Table II we have attempted to summarize our pathologic studies after triple coronary artery occlusion in all seven animal series There is clearly a great difference in right and left ventricular muscle mass damage between the control and the treated animal in the last two groups

The last two operations namely epicardiectomy sero pericardiectomy and the free omental graft alone or combined with internal mammary artery implantation operation were the only two procedures after which the animals had not only a high survival rate as shown in Table I but also a high survival rate of the ventricular muscle masses of both ventricles as shown in Table III

*Injection studies* The close correlation between animal survival after triple coronary artery occlusion and the development of extracardiac coronary anastomoses may be seen in the tabulation of coronary artery anastomoses shown in Table IV In this table the various anastomoses which developed are shown for those animal which died spontaneously and for those which were sacrificed for study Anastomoses have been graded as follows No anastomoses 0 Slight anastomoses + Moderate anastomoses ++ Extensive anastomoses +++

EXTRACARDIAC CORONARY ANASTOMOSES

*Table IV Tabulation of coronary extracardiac and mammary coronary anastomoses after triple coronary artery occlusion and revascularization surgery*

| | Number of animals in series | Animals dying spontaneously | | | | | | | Animals sacrificed | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Number of animals | Extracardiac mediastinal | | Intercoronary | | Homocoronary | | Number of sacrificed animals | Extracardiac mediastinal | | Intercoronary | | Homocoronary | |
| | | | +++ | ++ | +++ | ++ | +++ | ++ | | +++ | ++ | +++ | ++ | +++ | ++ |
| Control | 90 | 0 | 0 | 0 | 0 | 4 | 0 | 5 | | — | — | — | — | — | — |
| Treated | | | | | | | | | | | | | | | |
| 1 Epicardiectomy | 10 | 9 | 0 | 0 | 0 | | | 7 | 1 | 0 | 0 | 1 | 0 | 1 | 0 |
| 2 Epicardiectomy and sero-pericardiectomy | 10 | 8 | 0 | 0 | 0 | | 4 | 4 | [illegible] | 0 | 0 | | 0 | 2 | 0 |
| 3 Epicardiectomy and internal mammary artery implant | 10 | 6 | 0 | 0 IM | 0 | 1 | 1 | 5 | 4 | 0 IM | 0 IM | 3 | 1 | 4 | 0 |
| 4 Free omental graft | 10 | 6 | 1 | 0 | 0 | 0 | 0 | 0 | 4 | [illegible] | | 3 | 1 | 4 | 0 |
| 5 Epicardiectomy sero-pericardiectomy and free omental graft | 0 | 5 | 0 | 1 | 0 | 1 | | 3 | 15 | 4 | 11 | 5 | 9 | 11 | 4 |
| 6 Epicardiectomy sero-pericardiectomy free omental graft and internal mammary artery implant | 14 | 3 | 0 1 IM | 1 | 0 | 0 | 0 | 3 | 11 | 7 plus 8 IM | 4 plus 1 IM | 5 | 6 | 9 | |

IM Internal mammary co[illegible]nary anastomoses +++ Exte[illegible] anastomoses ++ Mod[illegible] [illegible]

Of the total of 94 animals (20 controls and 74 treated) 57 animals died spontaneously all within an average of 24 days 34 showed no extracardiac anastomoses (Fig 2) Thirty seven of the 74 treated animals survived and were sacrificed for study 13 of these showed extensive and 17 moderate extracardiac coronary anastomoses not including mammary coronary anastomoses

In Series 4 in which the free omental graft was simply wrapped around the heart



Fig 2 Roentgenogram of the heart of Animal No [illegible] which died after triple coronary artery occlusion by Ameroid constriction The animal was studied 19 days after surgery The only injection made was that through the thoracic aorta In this animal as in 34 of 37 animals which died spontaneously there was no evidence of the development of extracardiac coronary anastomoses

and the pericardium closed it was possible to fill the coronary arteries with injection mass through the aorta via the graft (Fig. 3).

In Series 5 in which only epicardiectomy and free omental graft were performed 15 of 20 animals survived and 15 had moderate to extensive extracardiac coronary anastomoses (Fig. 4).

The anastomoses referred to are those that form between the mediastinal vessels, pericardium, omentum and coronary arterioles. These are quite apart from the




Fig. 3. Roentgenogram of the heart of Animal No. 131 which died from a massive myocardial infarction in the right ventricle 25 days after placement of triple coronary artery Amerods and a free omental graft. The only injection made was that through the thoracic aorta. The extracardiac radiopaque injection showed the development of omental mammary-coronary anastomoses bringing the dye into the left coronary arterial system.

anastomoses formed between the implanted internal mammary artery and the myocardial arterioles (Fig 5) The latter are listed as separate anastomoses in Table IV thus in the two implant series there are anastomoses not only from the supplementary operative procedures but from the internal mammary artery itself

INTERNAL MAMMARY ARTERY IMPLANT WITH SUPPLEMENTARY OPERATIONS In Series 3 in which the internal mammary artery was combined with epicardiectomy there



Fig 4 Roentgenogram of the heart of Animal No 482 which survived triple coronary artery Ameroid occlusion epicardiectomy and free omental graft operation The animal was sacrificed and studied 469 days after surgery The only injection made was that through the thoracic aorta In this animal the injection mass filled the coronary arterial tree via the mediastinal-omental omental-coronary and omental myocardial anastomoses




Fig. 3. Roentgenogram of the heart of Animal No. 949 which had survived triple coronary artery occlusion by Ameroid, internal mammary artery implantation and free omental graft. The animal was studied 12 months after surgery. The only injection made was that through the thoracic aorta. In this animal the injection mass not only filled the coronary arterial tree via the mediastinal omental coronary and myocardial vessels but filled the internal mammary artery in retrograde manner as well.

were 6 patent mammary coronary anastomoses. Two of these animals died in these extensive intercoronary anastomoses had failed to form. In the 4 animals which survived there were extensive and moderate intercoronary anastomoses. When the omental graft was added to the internal mammary artery, 12 of 14 internal mammary arteries were patent. 11 of the animals survived and these showed moderate to extensive mammary coronary anastomoses. The internal mammary artery mammary coronary anastomoses were in addition to moderate and extensive extracardiac mediastinal coronary anastomoses which had been formed as a result of the free omental graft.

INTERCORONARY ANASTOMOSES. In none of the animals which died spontaneously, either the control or the treated groups, was there a single one which showed extensive intercoronary anastomoses (Fig. 6). On the right hand side of Table IV the findings in the animals which were sacrificed for study are recorded. Of the 37 animals which survived and were sacrificed for study there were 19 which showed extensive and 17 that showed moderate intercoronary anastomoses (Fig. 7).

**Discussion and conclusion**

The triple coronary artery Ameroid constriction test offers a reliable method of assaying a revascularization procedure. This simple test causes 100 per cent mortality in animals. There was massive myocardial damage in 17 of the control animals. A study of extracardiac coronary anastomoses and intercoronary anastomoses showed that nature failed to develop extracardiac coronary anastomoses. Likewise nature failed to develop extensive intercoronary anastomoses. The most that nature was capable of doing in response to occlusion of all three coronary arteries was to develop moderate intercoronary anastomoses.

Epicardiectomy and free omental graft proved to be effective in preventing death of the animal (75 per cent survival). It was likewise effective in protecting the



Fig. 6 [illegible]entg[illegible]ogram of the heart of Animal No. 1 4 which lived 17 days after tripl[illegible] Ameroid con[illegible]t[illegible]. The right [illegible]ry and then the left coronary artery were injected [illegible] The heart w[illegible] unrolled [illegible] x-rayed. Not[illegible] the almost complete [illegible]ence of interc[illegible]onary an[illegible]

# Case reports

## Cardiomegaly in myxedema

### Report of a case and review of the literature

*Edwin W. Monroe, M.D.**
*Eric L. Fearrington, M.D.*
*Greenville, N. C.*

Clinical and pathologic descriptions of cardiac abnormalities in myxedema have appeared in the medical literature for more than three quarters of a century. These began with a comprehensive review of *myxedema* by the Clinical Society of London in 1888.[1] The autopsy findings in 20 myxedematous patients were studied, including an examination of the heart in 9 cases. Two of these nine hearts were described as showing definite pathologic change— interstitial myocarditis. The concept of myxedematous heart disease as a distinct entity was initiated by Zondek in 1918 and defined more completely by Fahr[3] in 1925. Both authors observed and described dilated hearts, slow pulse rates, normal blood pressures, and low voltage on electrocardiograms in markedly myxedematous patients. These cardiac abnormalities demonstrated essentially a complete reversal to normal after treatment with thyroid.

Since those early attempts to define the cardiac status in myxedema, this matter has been the object of numerous case reports and periodic reviews. Many of these articles imply that myxedematous pericardial effusion is the sole cause of the clinical picture of "myxedema heart"—including the electrocardiographic and chest roentgenographic abnormalities. The purpose of this article is to present the case of a patient with massive cardiomegaly and pericardial effusion who probably also demonstrates primary involvement of the myocardium in severe myxedema. The literature as it pertains to cardiomegaly in myxedema is reviewed in order to re-examine the role played by pericardial effusion.

#### Case report

E. G., a 55-year-old Negro woman, was admitted to Pitt County Memorial Hospital for the first time on Sept. 7, 1962. A survey photoroentgenogram recorded 17 years previously had shown that *her heart was enlarged.* Fifteen years before admission she began to complain of mild dyspnea, orthopnea, and pedal edema. She was placed on digitalis, which she continued to take regularly. For 2 years prior to admission her dyspnea and edema progressed rapidly in spite of diuretics orally and by parenteral injection. For 17 years she had been aware of some fullness in the lower anterior region of the neck. She described dryness of her skin, partial alopecia, hoarseness, sluggishness, constipation, severe intolerance to cold, and loss of memory—all of these symptoms had progressed slowly over the past 15 years. She had been pregnant on one occasion 21 years previously with a normal delivery; this had been followed by normal menses until 17 years ago, when her menses stopped spontaneously at age 38. A gradual loss of weight of 30 pounds had occurred during the 15 years before this admission to hospital. A close friend of hers was known to have pulmonary tuberculosis. There was no history of angina, hypertension, renal disease, cough, fever, or night sweats.

Received for publication [illegible] 23, 1965.
*Address: [illegible] ille, N. C.



*Fig. 1.* Electrocardiogram recorded Sept. 10, 196[illegible] before treatment.

The physical examination on admission revealed an oral temperature of 99.8 F., pulse of 50 per minute and blood pressure of 140/86 mm. Hg. No paradoxical pulse was found. She was short (59 inches), plump (125 pounds) and pleasant but rather somnolent. Mild orthopnea was apparent. The skin was very dry and scaling; the hair was coarse and dry, and there was partial alopecia of the scalp. The tongue seemed to be slightly enlarged. The neck veins were flat. The thyroid gland was slightly enlarged; no nodularity was noted. The lungs were clear to percussion and auscultation. The cardiac examination revealed a barely palpable point of maximal impulse in the fifth left intercostal space 8 cm. from the midsternal line, whereas the left border of cardiac dullness extended into the left axilla. $A_2$ was louder than $P_2$. A Grade 1/6 harsh systolic murmur was heard in the second right anterior intercostal space parasternally; no gallop or rub was detected. The liver and spleen were not palpable. Moderate pitting edema was noted in the pretibial and pedal areas. No bruits were present over the abdominal aorta or the peripheral arteries. Her speech was slow and her voice was husky; her attention span was brief. The deep tendon reflexes exhibited a markedly prolonged relaxation phase.

Laboratory data included a negative VDRL, hemoglobin 8 Gm. per cent with the red blood cell described as normocytic and normochromic on the peripheral blood smear, white blood count 4,000 with a normal differential count; urinalysis revealed a specific gravity of 1.010 with one plus albuminuria; fasting blood sugar 92 mg. per cent, blood urea nitrogen 11 mg. per cent, serum sodium 130 mEq. per liter and serum potassium 4 mEq. per liter, serum albumin 2.9 Gm. per cent and serum globulin 2.1 Gm. per cent. The basal metabolic rate was −26 per cent. A serum cholesterol was 350 mg. per cent (normal in this laboratory 150 to 250 mg. per cent). The serum protein bound iodine was reported to be 0.7 μg. per cent. A 24 hour collection of urine for follicle stimulating hormone content was reported to be normal. An electrocardiogram revealed a normal sinus rhythm at 45 per minute with P-R 0.18 second, QRS 0.06 second and Q-T not measurable because of isoelectric T waves throughout; the QRS voltage was very low (see Fig. 1). The chest x-ray film showed a massively enlarged cardiac silhouette with no apparent pulmonary congestion (see Fig. 2).

*Course in the hospital.* The patient was thought to have myxedematous heart disease with pericardial effusion. She was continued on 0.1 mg. of digitoxin daily and a 700-mg. sodium diet. Because of the possibility of the presence of atherosclerotic coronary artery disease, thyroid extract was started slowly with an initial dosage of 16 mg. daily; this was cautiously increased to 64 mg. daily over the ensuing 4 weeks. At this point her objective [illegible]

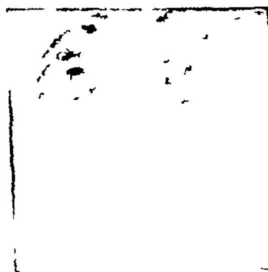


*Fig. 2.* Chest x-ray film taken Sept. 10, 196[illegible] before treatment.

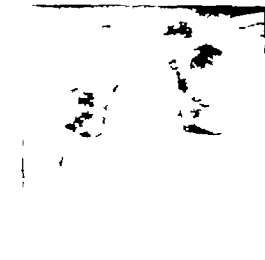


Fig 3 Chest x r film dated O t 3 1962—upright iew—after pericardiocentesis and in tillation of air into the pericardial sac

plaint of dy pnea had improved she had lost 6 pounds and had no edema A repeat PBI was 2 1 μg per cent However chest ray film showed that the cardiac silhouette was nchanged A pericardiocentesis was performed on Oct 3 1962 with the removal of 1 700 c c of turbid yellow fluid which did not clot This fluid was negativ on routine and acid fast culture and had a cholesterol ontent of 360 mg per cent and a protein ontent of 790 mg per cent Toward the end of the pericardiocentesis 300 c c of air was introduced into the pericardial sac A chest x ray obtained thereafter demonstrated that the massive cardiomegaly was due almost totally to the ast quant ty of pericardial fluid the pericardium was noted to be quite thin and the heart per se was probably normal in size (see Fig 3) On Oct 12 1962 another pericardiocentesis yielded 450 c of pink tinged yellow fluid The over all size of the cardiac silhouette was unchanged by the removal of this total of 1 650 c c of pericardial fluid However the patient noted marked improvement in her general state of well being and was allowed to go home on a regimen of 64 mg of th roid extract daily 0 1 mg of digitoxin daily and a 200-mg sodium diet Two weeks later he complained of increasing dy pnea and a dull constant aching discomfort in the anterior chest a low grade fever was present She was readmitted to Pitt County Memorial Hospital on Nov 16 1962 and remained there for 1 week Her temperature curve showed a da ly spike of 101 F orally The hemoglobin was 9 Gm per cent and the white blood count was 6 250 with a normal differential A PBI was 4 4 μg per cent The electrocardiogram showed improved QRS and T oltage with a sinus rate of 85 per minute no injury pattern was present A chest x ray film indicated that the massive cardiac ilhouette was unchanged and no pulmonary infiltration was apparent Because of the fever and a positive old tuberculin skin test in a 1 1000 dilution in this patient with continued massive pericardial effusion whose clinical myxedema had improved markedly she was transferred to Gravely Sanatorium Chapel Hill N C on Nov 23 1962 The presumptive discharge diagnosis was possible tuberculous pericarditis and myxedematous heart disease with pericardial effusion

*Summary of Gravely Sanatorium admission* The patient was admitted on Nov 23 1962 and discharged on Jan 24 1963 The history was that outlined above The physical examination revealed normal ital signs with a small goiter and mild continued evidence of myxedema This was manifested by dry and scaly sk with dry brittle hair and slight alopecia of the scalp the voice was husky the deep tendon reflexes continued to demonstrate a rather prolonged relaxation phase The lungs were clear and no edema or hepatomegaly was present *The left border of cardiac dullness extended into the left axilla* and the point of maximal impulse could not be located The previou ly described aortic systolic murmur was unchanged A pericardial rub wa not present

A summary of pertinent laboratory data included hematocrit 26 per cent on admis ion and 32 per cent on discharge WBC 6 150 with a normal *differential a normal urinalysis the blood urea* nitrogen serum electrolytes serum proteins and li er function studies were normal LE cell preparations were negative as were sputum studies and gastric washings for acid fast bacilli and for fungi An electrocardiogram on admission was similar to one obtained 12 days earlier during her second ad mi sion to the local hospital A chest x ray film continued to demonstr te massive cardiomegaly and cardiac fluoroscopy revealed only feeble pul ation of the heart borders

*Course in Gravely Sanatorium* The p tient was



Fig 4 Angiocardiogram dated J 11 1963 dem onstrating that cont nued cardiomegaly is now due to left ventricular enlargement

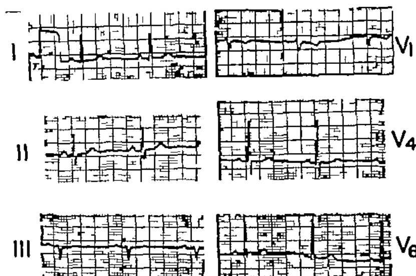



Fig 5 Electrocardiogram dated Nov 28 1964 This indicates virtually a complete return to normal



Fig 6 Chest x ray film dated Dec 5 1964 demonstrating the reversal to a normal cardiac silhouette

continued on salt restriction and 0 1 mg of digitoxin daily She was placed on isonicotinic acid hydrazide and para aminosalicylic acid as a therapeutic trial and as prophylaxis during her stay in the sanitorium The dosage of thyroid extract was increased to 120 mg daily The butanol-extractable iodine was 2 6 µg per cent on admission and rose to 4 5 µg per cent during her 2 month stay in the sanitorium Three days after admission 600 cc of pink tinged yellow fluid was obtained by pericardiocentesis This fluid was sterile on culture and showed no abnormal cells Several venous pressures and circulation times were normal The low grade fever disappeared during her first 2 weeks of hospitalization as did all of her subjective complaints However repeated chest x ray films showed no diminution in the size of the cardiac silhouette even though her thyroid status seemed to be normal clinically and by BEI measurement and the electrocardiogram demonstrated marked improvement in the voltage of the QRS and T wave A second pericardiocentesis was attempted on Jan 9 1963 and only 10 cc of fluid could be obtained Therefore a venous angiogram was obtained (see Fig 4) This demonstrated little if any residual pericardial fluid and delineated a markedly dilated heart—especially the left ventricle It was postulated that the continued cardiomegaly was due to myxedematous myocardiopathy The patient was removed from antitubercular therapy and discharged on digitoxin 0 1 mg daily thyroid extract 120 mg daily and a low salt diet

Since discharge from Gravely Sanitorium on Jan 24 1963 the patient has been seen at regular intervals In July 1963 she seemed to be mildly hyperthyroid she complained of nervousness and pounding heartbeat and her PBI was 7 6 µg per cent The thyroid dosage was reduced to 90 mg daily Since then she has remained well gradually resumed household activity and has been told by old friends that she appears to be years younger Over the past 2 years she has gained 25 pounds to a current weight of 136 pounds and her alopecia and other integumentary abnormalities have been completely corrected The PBI has ranged between 5 and 6 µg per cent The electrocardiogram has remained normal (see Fig 5) The enlarged cardiac silhouette has gradually returned to almost normal size a chest x ray film dated Dec 5 1964 showed a cardiothoracic ratio of 13 2–24 2 cm (see Fig 6) She has had no cardiac symptoms but the aortic

systolic murmur is unchanged and is thought to represent asymptomatic atherosclerotic involvement of the aortic valve.

## Review and discussion of literature

In 1949 Kern and associates[4] described pericardial effusion as being a constant, early, and major factor in the myxedematous heart. Four patients were reported with myxedematous pericardial effusions, and the authors stated that the resultant cardiac syndrome was due solely to the effusion and not contributed to by any myocardial change. They ascribed the cardiac silhouette on chest roentgenogram and the electrocardiographic changes to the presence of pericardial fluid and concluded that the heart itself was not enlarged or involved. Schnitzer and Gutmann had reached the same conclusions 3 years earlier when they reviewed the literature and added 1 case report to illustrate how commonly pericardial effusion is found in myxedematous hearts; this report also demonstrated that treatment with thyroid will cause the electrocardiographic and chest x-ray changes to revert to normal. In 1953 Marks and Roof reviewed 34 reported cases of myxedematous pericardial effusions and added 2 of their own. Both patients had large effusions but were not in congestive heart failure. These authors concluded that the pericardial effusion, as well as the less commonly found pleural and peritoneal effusions, were not due to primary myocardial insufficiency, since they responded so well to thyroid therapy alone.

The general subject of the heart in myxedema was reviewed in 1961 by Hamolsky[7] and Keating and associates. Both of these articles stressed the frequency with which pericardial effusions are found in the myxedematous heart and attributed the electrocardiographic abnormalities (low voltage, flat or inverted T waves, and occasional conduction defects) to the presence of the pericardial fluid. The electrocardiographic changes were observed to improve after pericardiocentesis. These authors also concluded that the roentgenographic finding of an enlarged cardiac silhouette was due to the pericardial effusion. The similarity of the clinical picture to that of congestive heart failure was discussed with the following differences noted: (1) the myxedematous patients had normal venous pressures and only rarely any evidence of lung congestion; (2) the pericardial fluid in myxedema had a high protein content, whereas the fluid of heart failure is low in protein; (3) digitalis does not improve the status of the myxedematous heart, but thyroid will cause it to revert to normal.[7]

The pathophysiologic derangements responsible for the collection of fluid in the serous cavities of a markedly myxedematous patient are poorly defined. A greatly increased capillary permeability has been found in such patients by Lange.[9] Renal clearance studies by Yount and Little[10] delineated a decrease in glomerular filtration, renal plasma flow, and renal blood flow, but the capacity of the patient with myxedema to excrete salt and water was noted to be normal. Hemodynamic studies by Scheinberg and associates[11] and by Graettinger and co-workers[1] demonstrated a low cardiac output in myxedematous patients. However, these studies also showed that oxygen consumption was low and thus the A-V oxygen difference at rest and with exercise was *not* relatively widened; this indicated that flow was proportional to the oxygen demands of the body. This contrasts with congestive failure, in which, along with a decreased cardiac output, the A-V oxygen difference is great—indicating more extraction of oxygen by the tissues per unit of blood flow, thereby compensating for the reduced flow. Ellis and associates[12] studied the hemodynamics of 5 myxedematous patients and found the cardiac output to be decreased and parallel to the decrease in oxygen consumption. Three of his patients had no increase in end-diastolic pressure such as is seen in heart failure, and the cardiac output increased with exercise—again differing from the response in heart failure. McBrien and Hindle[4] noted that the cardiac output decreased in 19 of 20 patients with myxedema during the Valsalva maneuver—similar to the response in a healthy heart—but no reflex slowing of the rate occurred, such as has been found to occur in the healthy heart. The other patient showed a heart failure response with no fall in pulse pressure

during the Valsalva maneuver this patient was noted to be in overt congestive failure

Descriptions of specific pathologic changes in the hearts of myxedematous patients are lacking. Various authors have described autopsy findings but these add little to the description of nonspecific myocarditis changes noted in 1888.[3] Since most of the patients dying with myxedema are elderly, many of the pathologic changes are contributed to by the aging process. Thus the fibrous tissue replacement in the myocardium noted by Brewer[16] and by Douglass and Jacobson[18] is also described in patients with progressive coronary artery disease. In myxedema the heart itself has been found to be pale, flabby, and dilated. There is interstitial edema in the myocardium which is seen microscopically as a faintly basophilic substance that is brilliantly P A S positive, high in protein and thought by Brewer[1] to be similar to the mucopolysaccharide of the ground substance. Goldberg[17] performed thyroidectomies on sheep and goats and at autopsy 2 years later found pericardial effusions surrounding hearts that were pale and flabby with microscopic disintegration of muscle fibers. In spite of these occasional reports of myocardial abnormalities noted in autopsied hearts, the impression persists in the literature that all of the available facts point to pericardial effusion as the factor primarily responsible for the clinical picture of the myxedematous heart.[4,7]

The ability of the chest roentgenogram and the electrocardiogram to determine whether abnormalities in these ancillary parameters of clinical evaluation were due solely to myxedema was explored by Aber and Thompson.[19] They evaluated 33 patients with clinical myxedema. Twenty-seven of these had electrocardiographic changes typical of myxedematous heart disease—low voltage and flat or inverted T waves. In the other 26 patients the electrocardiographic findings were not suggestive of myxedematous heart disease —5 had normal tracings, 11 had only very slight changes, 2 had a left bundle branch block, 2 had left ventricular hypertrophy, and 6 had evidence of severe coronary artery disease. The chest x-ray films of almost all of these same 26 patients showed an enlarged cardiac silhouette. In the 27 patients with electrocardiographic evidence of myxedema, chest x-ray films showed an enlarged cardiac silhouette in 14 and a normal heart size in the other 13. The authors concluded that the combination of an enlarged cardiac silhouette on chest x-ray films and an abnormal electrocardiogram implicated some underlying or associated cardiac disease in addition to clinical myxedema. Another tentative conclusion or interpretation could be reached on the basis of this study—at least one half of the patients with myxedema will have an enlarged cardiac silhouette on chest x-ray films along with an electrocardiogram showing typical changes of myxedema. And if the heart is enlarged on the x-ray film and the electrocardiogram does not show classic myxedematous change, some other cardiac disease should be suspected as the cause for the enlargement.

As mentioned earlier, many patients with myxedema have associated coronary artery disease.[7,8,18] However, angina pectoris is not a common symptom of untreated myxedema and if present it may disappear or improve with cautious thyroid replacement. Conversely, aggressive thyroid replacement may precipitate angina, especially in elderly myxedematous patients.[4] The entire concept of adult myxedema and its attendant hypercholesterolemia predisposing to premature or intensified atherosclerosis is open to critical re-evaluation and clarification.[3] A typical example of this presumed relationship is found in the autopsy series of Douglass and Jacobson[18] wherein coronary atherosclerosis was noted to a significant degree in all 10 cases of myxedema. However, the ages of the patients ranged from 63 to 78 years—ages at which coronary artery disease is prevalent even without myxedema.

The problem of ascertaining the presence of congestive failure in the patient with marked myxedema is a very real one, especially when one is confronted by peripheral edema, ascites, pleural effusion, marked cardiac enlargement on the chest x-ray film, and an electrocardiogram that shows bradycardia and very low voltage with widespread T wave flattening or inversion. This patient frequently is quite

dyspneic and orthopneic. If the venous pressure is normal and the chest x-ray film shows little or no pulmonary congestion, the physician can afford to begin thyroid replacement cautiously and observe the response. However, many clinicians feel obliged to reassure themselves that they are not dealing with an associated disease such as tuberculous pericarditis, pericardial effusion due to malignancy, etc. A pericardiocentesis can be performed with very little risk to the patient. If the fluid has a high content of protein and cholesterol and generally fits the criteria established for effusions in myxedema,[4,7] then watchful waiting to observe the response to thyroid therapy can be pursued. The negative reports from the acid-fast studies and cell blocks on the fluid reinforces the observant attitude.

Fortunately, the patient described in this case report represents a minority of the large group of myxedematous patients encountered in medical practice. However, it is a difficult minority to evaluate and manage. In such patients angiocardiography can be quite helpful in defining cardiomegaly—as shown by Kittredge and associates[27] and by the patient described in this case report. Newer techniques of evaluating cardiomegaly are being developed, such as gas injection,[33] radioactive isotope scanning,[34] and ultrasound.[35]

## Comments and summary

The case of a patient with long-standing, severe myxedema, including myxedematous heart disease, is presented. Two salient features are to be noted in this case report: (1) the massive cardiomegaly which was initially demonstrated to be due to a vast quantity of pericardial fluid and (2) continued massive cardiomegaly after all of the pericardial fluid had been removed or had resolved. The cardiac silhouette at this point was demonstrated by angiocardiography to be due primarily to left ventricular dilatation.

The literature pertaining to cardiomegaly in myxedema is reviewed and discussed. The trend in the literature of ascribing all of the features of myxedematous heart disease to pericardial effusion is questioned. Primary myocardial involvement in *severe* myxedematous heart disease would seem to have some role in the cardiomegaly of such patients.

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# The occurrence and mechanism of P-wave inversion in Lead I in right atrial overloading

## Report of two cases

U. Mirowski, M.D.
J. Lure, M.R.C.S. (Eng.), L.R.C.P. (Lond.)
Zerifin, Israel

Classically, inverted P waves in Lead I have been considered to be the most specific electrocardiographic sign of mirror image dextrocardia. Today, this concept is no longer justified. It has been shown that, due to left atrial rhythm, upright P waves in Lead I appear frequently in mirror image dextrocardia, whereas inverted P waves in this lead may be observed in patients with normally placed hearts.[1] Moreover, it has been postulated that inverted P waves in Lead I may also occur as a result of marked right atrial hypertrophy or dilatation[4] or in nodal rhythms.

Since the presence of negative P waves in Lead I in right atrial hypertrophy is not well documented in the literature, we thought it to be worth while to report 2 such cases. These observations are of particular interest because they provide convincing evidence of the causal relationship between the degree of right atrial overloading and the polarity of the P waves in Lead I. An explanation concerning the mechanism of this finding will be suggested.

In the electrocardiographic context of this report the terms right atrial hypertrophy, dilatation, and overloading will be used interchangeably.

## Case reports

*Case 1.* A 13-year-old boy was admitted to the pediatric department because he had had recurrent attacks of bronchial asthma for the previous few years. Between attacks the clinical picture was characterized by moderate pulmonary emphysema. An electrocardiogram recorded during a quiescent period (Fig. 1) showed signs of right atrial hypertrophy. The P waves were tall and peaked in Leads II, III, and aVF, reaching an amplitude of almost 2.5 mm. The P waves were upright in Lead I. The frontal P and QRS axes were +75 and +50 degrees, respectively.

Fig. 2 is an electrocardiogram recorded during an attack of asthma. The signs of right atrial overloading were significantly more pronounced than previously, with P waves in Leads II, III, and aVF having an amplitude of almost 3.5 mm. The P waves in Lead I became flat with the second part of it slightly inverted. Both the frontal P and QRS axes shifted to the right (+100 and +70 degrees, respectively).

*Case 2.* A 77-year-old man was admitted to the surgical department for prostatectomy. His past history was uneventful except for the fact that he had suffered for years from chronic emphysema and bronchitis. The clinical examination confirmed the presence of chronic lung disease. A routine electrocardiogram reproduced in the upper two rows of Fig. 3 showed evidence of right atrial hypertrophy with tall and peaked P waves having an amplitude of 3 mm in Leads II, III, and aVF. The P waves in Lead I were slightly inverted. The possibility of concomitant left atrial enlargement is suggested by the negative P wave in Lead V. The mean P and QRS axes were located in the vicinity of the +100 degree point in the frontal plane.

From the Division of Cardiology and the Department of Medicine B, Asaf Harofe Government Hospital, Zerifin, Israel.

Received for publication Sept. 3, 1963.

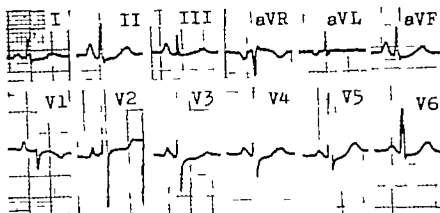



Fig. 1 Electrocardiogram of Case 1 showing presence of right atrial overloading. The P waves in Lead I are upright.

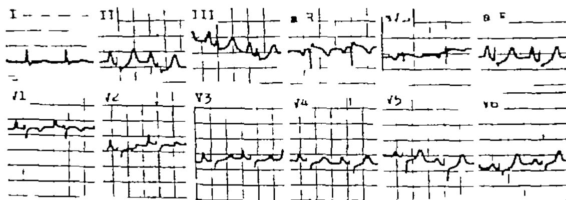



Fig. 2 Electrocardiogram of Case 1 taken during an attack of bronchial asthma. The P waves in Lead I have now become flat with their second part slightly inverted, whereas in Lead II, III and aVF they are taller than they were in Fig. 1.

In the bottom row of Fig. 3 are reproduced the limb leads recorded during a period when the patient's respiratory difficulties were particularly quiescent. The electrocardiographic evidence of right atrial overloading is now much less pronounced as demonstrated by the decreased amplitude of the P waves in Leads II, III and aVF. Simultaneously the P waves in Lead I became upright.

## Discussion

Although the P waves in right atrial overloading are usually tall and peaked in Lead II, III and aVF, they are of small amplitude in Lead I and occasionally may even become isoelectric.[9] Such changes are related to the increased magnitude and to a shift to the right of the resultant atrial vectors. It is accepted that this right deviation of the mean P axis is moderate and almost never exceeds the +90 degree position in the frontal plane,[8] a phenomenon which explains the usual absence of negative P waves in such cases. The fact that inverted P waves in Lead I do appear occasionally in right atrial overloading is evident from this communication.

In the cases presented above, the other possible causes of P wave inversion in Lead I were eliminated. Obviously there was no mirror image dextrocardia. Left atrial rhythm was excluded by analysis of the precordial lead which showed upright P waves over the left precordium.[1] The absence of retrograde P waves in the

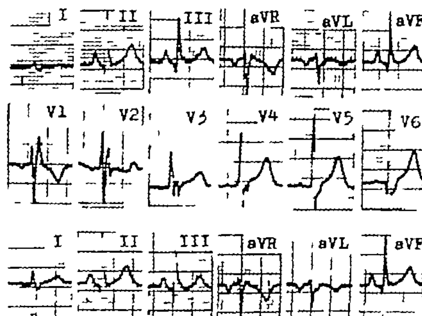



Fig. 3. Electrocardiogram of Case 2. *Upper two rows:* Note the slightly inverted P wave in Lead I and evidence of right atrial overloading. *Bottom row:* Limb leads recorded during a period of quiescence of the patient's respiratory condition. Note the upright P wave in Lead I. The P waves in Leads II, III, and aVF are not so tall nor so peaked as previously.

limb leads eliminated a nodal arrhythmia.

On the other hand, it is clearly demonstrated in our patients that an increase in right atrial overloading is accompanied by a flattening or even an inversion of the P waves in Lead I, whereas a decrease in stress on the right side of the heart is followed by a rise in the P waves to their original position.

It appears that the basic mechanism responsible for such changes is of a positional rather than a structural nature. This is indicated by the moderate shift of the mean P vector to the right, by the fact that such a shift is accompanied by a corresponding deviation of the QRS axis, and mainly by the transitory and reversible character of the electrocardiographic changes.

In order to explain the inversion of P waves in Lead I in right atrial overloading, it is not necessary to assume a shift of the mean P vector beyond the +90-degree position in the frontal plane. Such an assumption would be justified if the axis of Lead I were exactly horizontal, as postulated by Einthoven's equilateral triangle hypothesis. It is well known, however, that Einthoven's triangle does not represent accurately the anatomic and electrophysiologic facts and that the actual triangle is scalene rather than equilateral.[9,10] In this scalene or Burger's triangle the effective axis of Lead I is oblique, with a more or less pronounced inclination from the horizontal according to individual variations. Thus, a relatively moderate deviation of the P vector to the right, for example, from an average +50 degree position to a +75 degree position, may lead to a projection of this vector on the negative half of the effective Lead I axis and, consequently, to an inscription of inverted P waves in this lead (Fig. 4).

This explanation is supported by an analysis of the precordial leads. A deviation of the mean P vector beyond the +90-degree position means a change from the average right-to-left direction of activation to a left-to-right one and implies a simultaneous inversion of the P waves in Lead V₆, a lead similar to Lead I in its response to the transverse component of the dipole vector.[11] In our cases, however, the polarity of the P waves in Lead V₆ remained unchanged, whereas the P waves

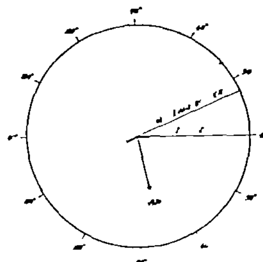


Fig 4 A diagram demonstrating that a P vector located in the vicinity of +75 or +80 degrees may be projected on the negative half of the effective (Burger) Lead I axis thus giving rise to inverted P wave in this lead For further explanations see text

in Lead I became inverted a phenomenon that is best explained by an obliquity of the Lead I axis as represented diagrammatically in Fig 4

The above presented explanation seems to be valid for both patients in spite of their widely different ages and in spite of the fact that the electrocardiogram of the second patient suggests other abnormalities such as left atrial enlargement and right bundle branch block


## Summary

Two cases of P wave inversion in Lead I due to right atrial overloading have been described It was demonstrated that the polarity of the P wave in Lead I is directly related to the degree of overloading on the right side of the heart


It was postulated that the negativity of the P waves in Lead I in right atrial overloading does not necessarily express a shift of the mean P vector beyond the +90 degree position in the frontal plane Because of the usual inclination of the effective Lead I axis from the horizontal in the Burger triangle a deviation of this vector to the right even though it still is less than +90 degrees may give rise to inverted P waves in Lead I

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# Origin of the right pulmonary artery from the aorta


*Harvey S Rosenberg MD**
*Grady L Hallman MD***
*Robert R Wolfe MD****
*Joseph R Latson MD*****
*Houston Tex*


The right pulmonary artery may arise from the aorta as a result of at least two different mechanisms In Type I (Fig 1 *A*) the proximal portion of the right sixth aortic arch is absent and the distal portion persists as a right ductus arteriosus forming a communication between the distal portion of the pulmonary artery and the innominate artery In Type II (Fig 1 *C*) a displaced septum in the embryonal truncus arteriosus results in an aortic origin of the right pulmonary artery near the base of the heart

In both types of abnormal origin of the right pulmonary artery the left lung is exposed to the entire output of the right ventricle if the intracardiac structure is normal With loss of the proximal portion of the sixth aortic arch (Type I) the communication with the distal portion of the pulmonary artery through a right ductus arteriosus is small resulting in a decreased flow of blood to and presumably a decreased pressure in the right lung When the embryonal truncal septum is displaced (Type II) circulation to the right lung is unimpeded and the lung is exposed to systemic pressures

Structural changes in the small pulmonary arteries result from both increased flow of blood and increased pressure When the right pulmonary artery arises from the aorta and the left pulmonary artery pursues its normal course the left lung is perfused with the entire output of the right ventricle at increased pressure where as the right lung is perfused with a normal or low flow at systemic pressure In either type of defect the left lung is exposed to high pressure at high flow and the right lung is exposed to normal or decreased flow at high or low pressure

## Case reports

*Case 1* The patient a critically ill 7 week old white male infant was hospitalized on May 7 1963 with cyanosis respiratory distress of 2 weeks duration poor feeding and diarrhea of 3 days

Physical examination revealed severe respiratory distress slight cyanosis and 10 per cent dehydration He had a weak cry and responded poorly to stimuli He weighed 8 pounds and 5 ounces and his temperature was 94 F Femoral and brachial pulses were present Mucous membranes were dry Sub

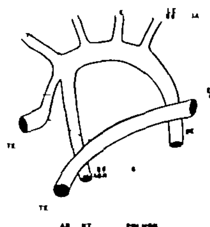

From the Departments of Pathology Surgery and Pediatrics Texas Children's Hospital and Baylor University College of Medicine Houston Tex

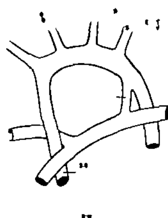


This study was supported in part by Grant HE-... from the National Institute of Health
Received for publication Sept 13 1963



*Associate Professor of Pathology and Pediatrics Baylor University College of Medicine Director of Laboratories Texas Children's Hospital 6621 Fannin St Houston Tex 77025
**Assistant Professor of Surgery Cora and Webb Mading Department of Surgery Baylor University College of Medicine
***Resident in Pediatrics Texas Children's Hospital and Baylor University College of Medicine
****Director of Cardiac Laboratories Texas Children's Hospital





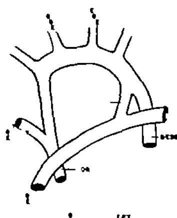


Fig. *1* Diagrams of th relationsh p of the pulmonary arteries and the aorta I Right patent d t t arterio us and absent right pulmonary artery (Type I defect) *B* Normal *C* Anomalous septati n of the truncus (Type II defect)

costal and substernal retractions accompanied respiration On auscultation of the lungs m ny crepitant râles were heard e pecially on the left The right ventricle w overs ti e and a Grade 2 (out of 4) short mid systolic ejection murmur was heard along the left sternal border The second pulmonic ound was narrowly split and louder than normal The liver was 5 cm below the right costal margin

Roentgenogram of the chest showed marked cardiac enlargement and congested lungs An ele trocardiogram revealed right axis deviation right atrial enlargement right ventricular hypertrophy and sinus tachycardia

The patient wa treated for heart failure with lanatoside C for dehydration w th intra enous fluid and for possible sepsi with penicillin and coli tin Despite these mea ures he died 2 hours after admi sion

At autop y the fingernail bed were cyanotic The lung were deep red purple and diffusely ede matou with only minimum aeration The right atrium and both the right and left entricles were dilated The great vessel arose from the ba e of the heart in their u ual relation hip but only the left pulmonary artery arose from the main pul monary artery (Fig 2) The systemic and pulmonary venou return were normal The foramen ovale was anatomically patent but valv compe tent The right pulmonary artery arose from the base of the left side of the aorta and passed pos teriorly to the right to reach the hilus of the right lung After giving rise to the pulmonary artery the aorta and its principal thoracic vessel ere normally formed The right ventricular wall was hypertrophic and mea ured 6 to 8 mm

In the left lung the media of the mall mu cular arteries was hypertrophied and the intima of the ela tic arteries was sclerotic The small arteries of the right lung were similar to those seen in normal infants of thi age (Fig 3 *A* and *B*)

*Case 2* A 13-day-old white male fant w hospitalized on Feb 18 1964 because of fast breath ing and cyanosi hich had been present since birth During the fir t trimester of pregnancy the mother had undergone exci on of a thyroglossal duct cyst A flu like illness had occurred shortly after the operation a d lasted for 2 weeks Delivery w unu eventful at full term

After an initial 3 min te period of apnea re pira tions were rap d and a sociated with retract H took feed ngs poorly C anosi leared and resp ratory tatus improved afte adm n tration of d gital and oxygen A heart murm ppeared 48 hour after b rth

On admission the inf t w pale and exh b ted respiratory distress w th resp tory rate of 100 per minute an l interco tal and ubcostal retr tions The pre ordial impulse eract ad the per beat forcef l the fifth terco tal pace t the anterior axill ry line The second heart ound in the pulmonary area a loosel split nd louder tha no mal A G ade 1 (out of 4) pan tol murmu t the lower left t rnal bord w followed by a shor t h gh frequency crescendo liastol mu mur At the apex th re w an ad d t on a lo pitched bort mid-dia tol c murmur







Fig 2 Case 1 *A* Viewed anteriorly only the left pulmonary artery arises from the main pulmonary artery The ductus arteriosus is patent *B* Viewed posteriorly the right pulmonary artery arises from the left a pect of the aorta and then passes posterior to the aorta to reach the hilus of the right lung *SVC* Superior vena cava *DA* Ductus arteriosu *LPA* Left pulmonary artery *RPA* Right pulmonary artery *MPA* Main pulmonary artery *PV* Pulmonary veins *RV* Right ventricle *LV* Left ventricle

The peripheral pul es were bounding and equal in the upper and lower extremities No râles were heard in the lungs The liver was soft and palpable 3 cm below the right costal margin There was no edema of the trunk or extremities

Roentgenograms of the chest showed that the heart was dilated with enlargement of all four chambers The pulmonary va cular markings were more prominent than normal The electrocardio gram indicated right ventricular hypertrophy S T segment change was considered to be related to the administration of digitalis Hemogram and urinalysis were normal for his age

Since the infant would not tolerate an environ ment of room air cardiac catheterization was per formed on the day after admission with the baby breathing *100 per cent oxygen Morphine and* atropine had been admini tered as premedication Right brachial arterial oxygen saturation was 98 per cent Right entricular and pulmonary systolic pres ure were greater than systemic arterial pres sure Left atrial pressure was elevated (35/15 mm Hg) and higher than right atrial pressure *(20/10* mm Hg) Cardio Green dye curves with sampling from the right brachial artery after injection into the main pulmonary artery right ventricle and inferior ena cava showed a small right to left shunt and a large left to right shunt Only a left to right shunt was demonstrated by injection into the left trium An angiocardiogram obtained via a catheter passed through a patent foramen ovale into the left atrium showed that the right pulmonary artery arose from the ascending orta (Fig 4)

Surgical therapy was elected because of the critical status of the patient due to intractable cardiac failure in spite of treatment with digitali nd oxygen An attempt at decreasing the magni tude of the left to right shunt was considered to be advisable and constriction or ligation of the anoma lous right pulmonary artery was planned

Operation was performed shortly after the com pletion of cardiac catheterization A left patent ductus arteriosus 7 mm in diameter was doubly ligated The left pulmonary artery arose normally from the main pulmonary trunk The right pul monary artery was 4 mm in diameter and arose from the right side of the ascending aorta 1 5 cm above the aortic anulus Becau e the small size of the anomalous right pulmonary artery made it unsuitable for grafting or anastomosi it was li gated near ts point of origin in order to interrupt the left to right shunt through the lungs Cardiac action appeared to be satisfactory The pericardium was closed loosely and the thoracic incision repaired After the infant arrived in the recovery room his condition deteriorated and death occurred 3 hours after operation

Postmortem examination revealed no intra cardiac anomalies The foramen ov le was val e competent The main pulmonary artery gave rise to only one branch the left pulmonary artery The right pulmonary artery arose from the ascending aorta 1 5 cm above the anulus followed a normal distribution and had been ligated near the aorta The ductus arteriosus had been patent but wa occluded by ligatures

On microscopic examination the lungs were

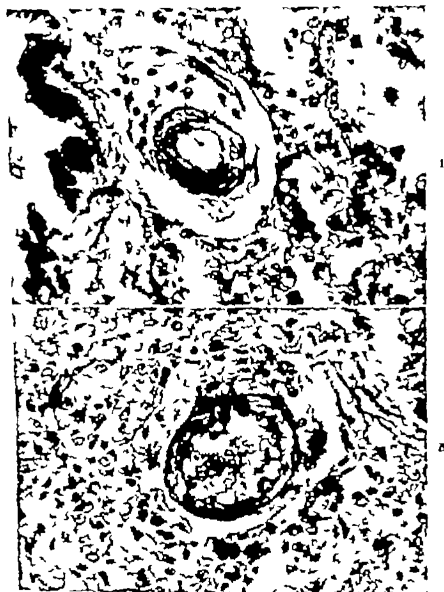


Fig. 3. Case 1. In the left lung (*A*) the media is relatively thick, whereas in the right lung (*B*) the proportion of media to the entire wall is normal. (Verhoeff-Van Gieson. ×160.)

found to be edematous and filled with alveolar histiocytes. Medial hypertrophy of the small muscular pulmonary arteries was noted in both lungs which were comparable to those of normal infants of the same age (Fig. 3, *A* and *B*).

*Case 3.* This 5 month-old white male infant had had a heart murmur at birth but he did well until the age of 2½ months when he developed labored and noisy respirations intermittently. Cyanosis was slowly progressive and especially marked with effort.

On physical examination the infant was cyanotic with noisy respiration, intermittent expiratory stridor, and a brassy cough that was markedly accentuated with effort. Vital signs were: heart rate 160 per minute; respirations 56 per minute; blood pressure (right arm) 110/0, (left arm) 110/0, and (left leg) 118/0 mm. Hg. He weighed 13 pounds and 3 ounces, which placed him between the third and tenth percentiles for weight. The neck veins were slightly distended. There was a precordial bulge with a prominent Harrison groove. Breath sounds were harsh bilaterally. The point of maximum impulse was in the sixth intercostal space midway between the midclavicular and the anterior axillary lines. There was a thrill over the lower left sternal border and a precordial and xyphoid thrust. A to-and-fro Grade 4 (out of 6) systo-diastolic



Fig 4 Angiocardiogram with injection of contrast material into left atrium Note the origin of the right pulmonary artery from the right side of the ascending aorta

murmur was heard along the lower left sternal border with apical mid diastolic flow murmur A continuous murmur was heard at the base of the heart with high pitched diastolic murmur An ejection click was heard at the lower left sternal border and apex The liver was palpable 5 to 6 cm below the right costal margin

An ECG showed a frontal QRS axis of positive 130 degrees and right atrial enlargement and right ventricular hypertrophy Chest x ray films showed moderate to marked cardiac enlargement with slight concavity of the pulmonary artery segment There were increased pulmonary vascular markings and a prominent thymic shadow at the right base

A cardiac catheter passed from the right ventricle into the aorta and then into the pulmonary artery without re entering the right ventricle The pulmonary arterial oxygen saturation was persistently greater than the systemic arterial oxygen saturation Right and left ventricular pressures were equal An oxygen saturation step up occurred between the middle and the outflow tract of the right ventricle just beneath the valve

An esophagogram showed displacement of the esophagus and trachea to the right and upward The baby's respiratory distress increased and digitalization was begun

Severe cardiac failure was apparently due to a large left-to-right shunt Because of the critical condition of the patient and lack of response to medical therapy operation was considered to be advisable in order to decrease the magnitude of the shunt

Operation was performed 3 days after catheterization The pulmonary branch of the truncus was banded The child's respiratory difficulty increased and he died on the day after operation

At autopsy a truncus arteriosus arose from the base of the heart The left pulmonary artery arose from the base of the truncus but the orifice of the right pulmonary artery was much higher arising from a small branch which extended from the base of the innominate artery to the hilus of the right lung (Fig 6) Bronchial arteries with an external diameter of 2 mm extended to the hilus of the right lung

Within the heart a defect in the interventricular septum was anterior to the crista supraventricularis The valve of the truncus arteriosus had three cusps which were slightly thickened

The vessel from the innominate artery to the hilus of the right lung was interpreted as a right patent ductus arteriosus The wall was thicker and the lumen narrower than those of the left pulmonary artery or the distal portion of the right pulmonary artery

Microscopically the small muscular arteries of the left lung showed medial hypertrophy whereas those on the right had a relatively thin media (Fig 7 A and B)

## Discussion

In the human embryo the definitive pulmonary arteries are formed by the ventral (proximal) rudiments of the sixth aortic arch The distal (dorsal) components of the sixth arch connect the ventral rudiments with the dorsal aorta and constitute the ductus arteriosus on each side Normally the distal portion of the right sixth arch (i e the right ductus arteriosus) disappears and the proximal portion persists as the proximal part of the right pulmonary artery[1] Should development be abnormal with persistence of the distal portion and disappearance of the proximal portion of the sixth right aortic arch the right pulmonary artery would arise from the aorta through the medium of a persistent right ductus arteriosus forming a Type I origin of the right pulmonary artery from the aorta

The embryonal truncus is separated into an aortic and pulmonary artery component by a spiral septum Whereas absence of this septum results in a persistent truncus arteriosus displacement of the septum results in the Type II origin of the right pulmonary artery from the aorta at the base of the heart

The Type I defect was described by Wagenvoort and associates in a 20 day old infant They found a right pulmonary artery arising from the aorta with the

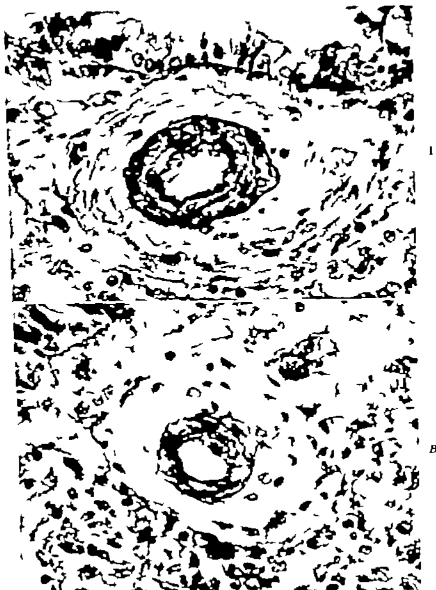



Fig 5 Case 2 The media is prominent in the small muscular arteries of the right lung (*A*) as well as in those of the left lung (*B*) (Verhoeff Van Gieson ×160 )

proximal portion made up of ductus like tissue indicating the persistence of the distal portion of the sixth arch and loss of the proximal portion

In 1963 Odell and Smith[3] reported 3 instances of patients with aortic origin of the right pulmonary artery and found mention of 11 others in the literature The age of these patients at death was 4 months or less in 70 per cent Pathologic data were available on 13 patients There were 10 Type II cases with the right pulmonary artery arising from the ascending aorta and 3 Type I cases in which the pulmonary artery arose from the base of the innominate artery Among the 8 patients in whom exact size was specified the right pulmonary artery was [illegible] mm or greater in 5 A majority of patients (8 of 13) had an associated patent ductus arteriosus One patient had an aorticopulmonary window 1 had a right subclavian artery




Fig 6 Case 3 A surgically placed band surrounds the left pulmonary artery near its origin from the truncus The proximal right pulmonary artery is absent The ductus extends from the innominate artery to the hilus of the right lung D1 Ductus arteriosus LP1 Left pulmonary artery T1 Truncus arteriosus

arising from the ascending aorta and 3 had no associated anomalies

Physiologically an anomalous right pulmonary artery of either type functions as a left to-right shunt much as does a patent ductus arteriosus or ventricular septal defect This shunt plus that through a frequently associated patent ductus account for the severe heart failure seen in patients with this anomaly and may explain the short lifespan of individuals so afflicted

The pulmonary arterial bed responds with a series of reactions to increased blood flow when the pressure is high as in the case of a ventricular septal defect A similar vascular response is usually delayed for many years when the increased flow is under low pressures as in the case of an atrial septal defect

Even with ventricular septal defects there is no direct correlation between pulmonary arterial structure and pulmonary blood pressure or flow [4] In general pulmonary hypertension with an increased blood flow is associated with medial hypertrophy of the small muscular arteries whereas pulmonary hypertension and decreased pulmonary blood flow are associated with intimal sclerosis [3]

In the Type II defect or abnormal truncal septation the right lung is subjected to normal or low flow at systemic arterial pressure whereas the left lung is subjected to an increased flow consisting of the entire output of the right ventricle probably at an increased pressure

Odell and Smith[9] found no consistent pattern or pulmonary vascular structures correlating with either high pulmonary arterial flow or pressure in their review of cases with recorded pulmonary histology however 3 cases were altered by narrowed proximal portions of the right pulmonary thus possibly shielding the small pulmonary vessels from systemic arterial pressure It is likely that those cases with small right pulmonary arteries were actually examples of Type I defects in which the right lung is perfused through a persistent right patent ductus arteriosus

In our Cases 1 and 2 the malformation was Type II in each with widely patent right pulmonary arteries allowing unobstructed exposure of the right lung to systemic pressure In Case 1 the media of the vessels of the left lung was thicker than that of the vessels of the right lung This difference was considerably more prominent in Case 1 who lived to 7 weeks of age than in Case 2 who lived to the age of 2 weeks This relative minor difference between the lungs in Case 2 would be expected because of the thick medial layers normally present in the first months of life The catheterization data from Case 2 reveal the presence of pulmonary hypertension Thus the pulmonary vascular bed of the left lung appears to have responded to increased flow and pressure by medial hypertrophy of small muscular arteries but the vascular bed of the right lung responded little or not at all to increased pressure with normal flow In Case 3 in which the right pulmonary




Fig. 7. Case 3. *A*, The medial layer of the small muscular arteries of the left lung is hypertrophic. *B*, In the left lung the media is thin. (Verhoeff-Van Gieson. ×160.)

artery arose from a ductus, the pulmonary arteries of the right lung had very thin walls, whereas those of the left lung showed medial hypertrophy.

Surgical treatment of a right pulmonary artery arising from the aorta should aim at interrupting the shunt and then, ideally, at restoring normal flow by anastomosing this vessel to the main pulmonary artery by means of a graft. Ligation of the right pulmonary artery or pneumonectomy for treatment of the origin of the right pulmonary artery from the aorta was first suggested by Findlay and Maier,[6] who reported the case of a 4 month old infant with this anomaly who died from heart failure and pneumonia. Later, Maier[7] mentioned the possibility of anastomosing the anomalous right pulmonary artery to the main pulmonary trunk. In 1957 Caro, Lermanda, and Lyons reported an operation upon a 23 year old man with aortic origin of the right pulmonary artery and a patent ductus arteriosus (Table I). After

*Table I. Surgical treatment of patients with right pulmonary artery arising from aorta*

| *Author* | *Age of patient* | *Diagnosed preop.* | *Operation* | *Results* |
|---|---|---|---|---|
| Caro et al. | 23 yr. | Yes | Interruption of PDA. Anastomosis of RPA to MPA by means of Ivalon graft | Died from hemorrhage from lacerated intercostal vessel |
| Armer et al. | 10 mo. | Yes | Interruption of PDA. Anastomosis of RPA to MPA by means of Dacron graft | Survived |
| Mad et al. | 4 mo. | Yes | Interruption of PDA. Ligation of RPA | Dramatic relief of heart failure. Died 4 weeks later of pneumonia |
| DuShane et al. | 2 mo. | No | Interruption of PDA | Died |
| Rosenberg et al. | 2 wk. | Yes | Ligation of PDA. Ligation of RPA | Died |

*PDA*, Patent ductus arteriosus; *RPA*, Right pulmonary artery; *MPA*, Main pulmonary artery.

closure of the ductus, the right pulmonary artery was detached from the aorta and anastomosed to the main pulmonary artery by means of an Ivalon graft. Unfortunately, the patient died 5 hours after operation from hemorrhage into the left chest, apparently from a lacerated intercostal artery. The first successful operation for total correction of this anomaly was reported by Armer, Schumacker, and Klatte,[3] who anastomosed a 13 mm. anomalous right pulmonary artery to the main pulmonary trunk in a 10 month old patient by means of a 13 mm. Dacron tube graft. A 7 mm. patent ductus arteriosus was divided and sutured. Armer and associates cite Mad and Lambert,[4] who made a correct diagnosis of this anomaly by cardiac catheterization and angiocardiography in a 4-month-old infant. Closure of a patent ductus arteriosus and ligation of the anomalous right pulmonary artery resulted in dramatic relief of heart failure, but the infant died 4 weeks later from pneumonia. DuShane and associates[5] reported the case of a 2 month old infant with heart failure and cyanosis. A diagnosis of patent ductus was made by cardiac catheterization; angiocardiography was not performed. Operation consisted of division and suture of a patent ductus arteriosus and death occurred the next day. At autopsy, the right pulmonary artery, 1 cm. in diameter, was found to arise from the ascending aorta.

The value of selective angiocardiography in the diagnosis of aortic origin of the right pulmonary artery cannot be overemphasized. Cardiac catheterization may fail to detect this anomaly, and precise anatomic delineation by angiographic techniques is necessary. The poor prospect of survival makes operative therapy mandatory in the face of intractable heart failure. Closure of the commonly associated patent ductus would not be expected to control cardiac failure in most instances, and ligation of the right pulmonary artery is required to interrupt the left-to-right shunt. Unilateral pulmonary artery ligation is compatible with survival,[1] and may be all that is technically feasible if the anomalous pulmonary artery is less than 5 or 6 mm. in diameter. If the anomalous pulmonary artery is greater than 5 or 6 mm. in diameter, it should be anastomosed to the main pulmonary trunk by means of a Dacron tube graft of suitable size. If a grafting procedure is not feasible, consideration may be given to anastomosing the right pulmonary artery to the superior vena cava.

**Summary**

Origin of the right pulmonary artery from the aorta is a rare anomaly that may produce heart failure and death in early infancy. The lesion may result from two different developmental defects abnormal septation of the primitive truncus or atresia of the proximal portion of the sixth right aortic arch and persistence of the distal portion as a right ductus arteriosus. The clinical and pathologic findings in 3 infants with this defect are described. The value of precise diagnostic studies especially selective angiocardiography is emphasized. Surgical treatment should be directed at interruption of the left to right shunt by ligation of the right pulmonary artery and if possible this vessel should be anastomosed to the main pulmonary trunk by means of a Dacron graft.

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## Postperfusion syndrome

### A review and report of 21 cases

*J. A. Reyman, M.D.**
*Detroit, Mich.*

The appearance of atypical lymphocytes in the blood of patients after open heart surgery was first described by Battle and Hewlett[1] in 1958. In 1960 Kreel and associates[2] reported a syndrome consisting of fever, splenomegaly, and atypical lymphocytes in the blood of patients who were operated on for cardiac disease using the cardiopulmonary bypass technique. Subsequently, seven additional reports appeared describing 58 similar cases.[3-9] The present study deals with 16 cases of this syndrome and the cases of 5 other patients who probably had this illness. A necropsy report is included on one patient who developed this disease and died from other causes.

#### Data

At Harper Hospital from July, 1959, through April, 1965, 380 major cardiovascular operations were performed utilizing cardiopulmonary bypass technique. Survival data are summarized in Table I. Fifteen of these patients were noted to develop typical postperfusion syndrome (febrile lymphocytic splenomegaly) characterized by an elevation of temperature from 100 to 103°F., with atypical lymphocytes in the peripheral blood (Table II). Splenomegaly was present in 12 patients and was never severe. Malaise was not a prominent symptom and none of the patients complained of chest pain. In 2 patients (Cases 12 and 21) transient non-exudative pharyngitis and shotty lymphadenopathy were noted on physical examination. The first of these patients also had a nonpruritic maculopapular rash which persisted for only 36 to 48 hours.

Hepatomegaly was noted in 4 patients. Hepatic function tests were abnormal in 7 of 15 patients; most commonly there were mild to moderate elevations of the serum glutamic oxalacetic transaminase (SGOT) and/or lactic dehydrogenase (LDH). One patient (Case 7) had rather severe hepatitis during the course of the postperfusion syndrome, with associated malaise and jaundice. Preoperatively, the Bromsulphalein retention had been slightly elevated at 12 per cent. Postoperatively, she did well until the onset of postperfusion syndrome, at which time she became jaundiced and the hepatic function tests were as follows: bilirubin 3.7 mg. per 100 ml. (direct) and 6.0 mg. per 100 ml. (total); cephalin flocculation 3+ and 4+ at 24 and 48 hours; thymol turbidity 26 units; and Bromsulphalein retention 38 per cent. Overt signs and symptoms of both hepatitis and postperfusion syndrome disappeared within 2 weeks, although mild hepatic chemical abnormalities persisted longer.

Received for publication Oct. 2, 1965.
*From the [illegible] Department of [illegible] Hospital [illegible] School of Medicine, Detroit, Mich. [illegible]

*Table I Survival data on 380 operative cases using cardiopulmonary bypass*

| *Cardiac disease* | *All cases* | *Number of survivals* | *Per cent* |
|---|---|---|---|
| Congenital | | | |
| Male | 71 | 57 | 80 3 |
| Female | 85 | 66 | 77 6 |
| Subtotal | 156 | 123 | 78 8 |
| Acquired | | | |
| Male | 80 | 46 | 57 5 |
| Female | 144 | 98 | 68 1 |
| Subtotal | 224 | 144 | 64 3 |
| Total | 380 | 267 | 70 3 |

In Case 11 malaise was noted during the course of the postperfusion syndrome and hepatic function tests revealed an SGOT of 150 units LDH of 1 015 units and cephalin flocculation of 3+ and 4+ at 24 and 48 hours Bilirubin was normal Plasma hemoglobin was 7 mg per 100 ml and erythrocyte sedimentation rate was 39 mm per hour In Case 4 the results of the tests of hepatic function were as follows bilirubin 0 1 mg per 100 ml (direct) and 0 6 mg per 100 ml (total) cephalin flocculation 2+ at 24 and 48 hours alkaline phosphatase 15 King Armstrong units and Bromsulphalein retention 10 per cent In both instances the hepatic function was either improved or normal when the patient was discharged

The number of lymphocytes in the blood of these patients varied from 25 to 79 per cent of the total white blood cells with atypical or Downey cells ranging

*Table II Data on patients with postperfusion syndrome*

| *Case* | *Age (yr) Sex* | *Blood type* | *Cardiac disorder* | *Onset (days)* | *Fever* | *Splenomegaly* | *Hepatomegaly* | *WBC* | *Lymphocytes (%)* | *Atypical lymphocytes (%)* | *Heterophil titers* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 15 M | O− | VSD PS | 36 | + | + | + | 7 [illegible]00 | 5[illegible] | 21 | 1 78 |
| 2 | 15 F | O+ | VSD PS | 18 | + | + | − | 10 [illegible]00 | 67 | 22 | 1 7 |
| 3 | 9 F | O+ | VSD PS | 23 | + | + | − | 8 200 | 61 | 14 | — |
| 4 | 1[illegible] F | B+ | VSD | 29 | + | − | + | 7 650 | 46 | 14 | 1 28 |
| 5 | 5 M | A+ | ASD | 19 | + | + | − | [illegible] 300 | 6[illegible] | 20 | 1 14 |
| 6 | 18 M | B+ | ASD PS | 27 | + | + | − | 5 300 | 58 | Almost all | Negative |
| 7 | 39 F | A+ | MS | 15 | + | + | + | 7 000 | 69 | Almost all | 1 7 |
| 8 | 58 M | A+ | TAA | 37 | + | − | − | 7 600 | 34 | 10 | Negative |
| 9 | 28 F | A+ | AS,AI | 34 | + | + | − | 5 600 | 52 | 19 | 1 11[illegible] |
| 10 | 33 F | O+ | TF | 37 | + | − | − | 3 900 | 59 | 19 | 1 14 |
| 11 | 16 F | O+ | VSD | 27 | + | + | − | 4 900 | 55 | 19 | 1 14 |
| 12 | 28 F | B− | MI | 35 | + | − | − | 7 600 | 45 | 3 | — |
| 13 | 39 M | B+ | ASD | 14 | + | − | − | 9 000 | 37 | 7 | — |
| 14 | 23 M | A+ | ASD | 21 | + | + | − | 4 200 | 40 | 16 | 1 14 |
| 15 | 37 F | A+ | ASD | 15 | + | + | − | 5 600 | 5 | 3 | — |
| 16 | 13 F | AB+ | VSD PS | 27 | + | − | − | 9 600 | 50 | Few | — |
| 17 | 37 F | A+ | ASD | 33 | + | − | − | 8 100 | 60 | Few | — |
| 18 | 8 M | O+ | ASD | 14 | + | − | − | 7 400 | 5 | None | — |
| 19 | 21 F | O− | ASD | 15 | + | + | + | 7 300 | 38 | None† | — |
| 20 | 3[illegible] F | O+ | MS | 18 | + | + | − | 6 800 | 46 | None† | — |
| 21 | 23 M | O+ | None | 31 | + | Splenectomy | − | 23 300 | 9 | 60 | Negative |

VSD Ventricular septal defect, ASD Atrial septal defect, P[illegible] [illegible], MS Mitral [illegible], MI Mitral insufficiency, AS AI Aortic [illegible] and insufficiency, TF T[illegible] [illegible], TAA [illegible]

† [illegible] not reported [illegible]

†† [illegible] rupture of spleen [illegible] accident.

from 3 to 60 per cent. Total white blood cell counts were normal in 19 patients with leukocytosis of 10,700 and 23,300 per cubic millimeter in the other 2 patients. Absolute neutropenia was noted in many patients with a marked shift to the left which included the appearance of myelocytes and promyelocytes. Eosinophilia was found in 2 patients (Cases 10 and 21); it ranged from 6 to 11 per cent.

Hemoglobin, hematocrit and total red blood cell counts showed corresponding values and were either normal or mildly decreased. In those patients in whom they were low, there had been a slow decline from the immediate postoperative period with stabilization and no decrease during the acute phase of the postperfusion syndrome. Reticulocyte counts in 6 of these patients revealed a range from normal (less than 2.5 per cent) to a maximum of 6.4 per cent. Normoblasts were noted in 2 patients. Platelet counts in 3 patients showed normal or slightly increased values. *Heterophil agglutination titers determined* in 12 of the 15 patients were nondiagnostic. In Case 9, the titer was 1:112, but differential absorptions were not positive (guinea pig kidney 1:28 and beef red cells 1:14).

*Multiple blood cultures were performed* on all of these patients and were negative for bacteria and fungi.

In 5 other patients the classic triad of *signs and symptoms was variably present* (Cases 16 through 20). All had intermittent fever and 2 had splenomegaly. Atypical lymphocytes were present in small numbers or were not reported from smears of peripheral blood, although slides were not available for review. The delayed onset of signs and symptoms with a normal white blood cell count and lymphocytosis suggests that these patients belong in this disease group.

Two of the 21 patients had not undergone cardiopulmonary bypass. The first, Case 8, had been subjected only to left ventricular bypass without artificial oxygenation during operation for a thoracic aortic aneurysm. The second patient (Case 21) had had a ruptured spleen removed after an automobile accident, and no cardiopulmonary bypass had been used. It is interesting that this asplenic patient had the highest white blood cell count, the greatest number of lymphocytes, and the greatest number of Downey cells. The SGOT was 66 during the course of the illness, and heterophil titers were negative on three occasions.

Cardiac disease in the first 20 patients consisted of 15 cases of congenital defects, 5 cases of rheumatic valvulitis, and the 1 case of thoracic aortic aneurysm. The patients with congenital heart disease made up 75.0 per cent of the cases of postperfusion syndrome, and the patients with acquired heart disease comprised only 25.0 per cent.

The onset of signs and symptoms varied from 14 to 37 days postoperatively and persisted from 1 to 4 weeks. In general, the *fever subsided first*, and the splenomegaly and the atypical lymphocytes in the peripheral blood remained the longest, although usually not more than a month after the patient had been discharged from the hospital.

*However, one patient (Case 1) developed* congestive heart failure 16 days postoperatively; it was partially controlled with digitalis and diuretics. Thirty-six days after operation he developed typical postperfusion syndrome. Five days later he *died from intractable heart failure*. Necropsy revealed fibrinous pleuritis and pericarditis, and further examination of the heart showed that the Teflon graft *had torn loose from the site of repair of* the ventricular septal defect and that a 4 cm. opening was present. Mediastinal lymphadenopathy was present. The liver weighed 2,000 grams and had a prominent lobular pattern. The spleen weighed 580 grams with bulging red soft parenchyma that had a decreased follicular pattern. Microscopically, the heart showed fibrous and granulation tissue near the site of septal repair. The liver revealed chronic passive congestion with nucleated red blood cells in the sinusoids. An inflammatory infiltrate was noted in the portal areas and consisted chiefly of large and small mononuclear cells. The spleen exhibited small lymphoid follicles, some of which had germinal centers. The red pulp was congested, and the trabeculae were partially obscured by large and small mononuclear cells. *The vessels and capsule*

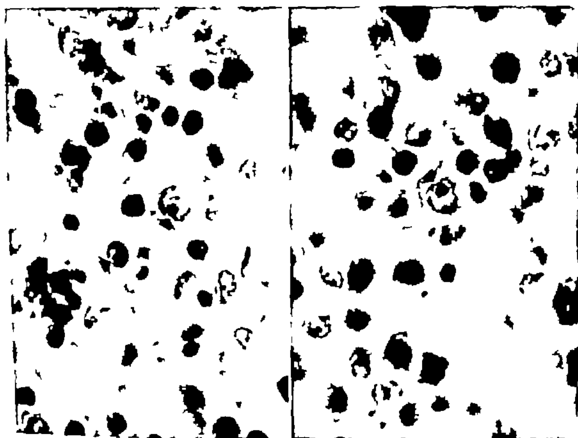


Fig 1 Sections of the spleen from a patient with postperfusion syndrome reveal several large basophilic mononuclear cells within the sinusoids which contain phloxine positive inclusion like masses within the nuclei (arrows) resembling viral inclusion bodies. Similar inclusions were noted in the cells of the lymph nodes (Phloxine hematoxylin ×1 710)

were normal. Phloxine hematoxylin stain revealed phloxine positive slightly irregular structures within the nuclei of many of these cells. These masses were distinct from the chromatin and nucleoli and resembled inclusion bodies (Fig 1). The lymph nodes contained similar cells which had these inclusions within the nuclei. The bone marrow was hyperplastic with an apparent increase in the erythroid series.

**Discussion**

A résumé of the findings in the 82 reported cases of postperfusion syndrome (Table III) reveals a wide variety of normal as well as abnormal diagnostic laboratory examinations. Tests of hepatic function revealed elevated levels of SGOT, SGPT and LDH, most of which were mild and transient [illegible]. Also high values were noted for thymol turbidity [illegible] cephalin flocculation [illegible] alkaline phosphatase and Bromsulphalein retention. Similar abnormalities were noted in this study, and the development of jaundice in one patient in the present series has not been reported previously. These data suggest that there is a hepatic component to the postperfusion syndrome, although the chemical abnormalities might be a result of operative cardiac injury in some cases. The findings in the patient who had only splenectomy and a SGOT of 66 units, as well as the more severely deranged values in other cases noted in this study, tend to support the former explanation.

Hematologic abnormalities other than those previously described are apparently not common or consistent. Leslie and Glenn noted eosinophilia in their 3 cases and 2 patients in this study also had high

*Table III. Summary of data on reported cases of postperfusion syndrome*

| Item | Series number 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Total | Per cent |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of cases | 1 | | 6 | 3 | 11 | 14 | 1 | 9 | 14‡ | 21 | 82 | 100 |
| Fever | † | | 4 | 3 | 11 | 14 | 1 | 7 | 14 | 21 | 75 | 91.4 |
| Splenomegaly | | 1 | 6 | 3 | 7 | 12 | – | 9 | 7 | 12 | 57 | 69.5 |
| Hepatomegaly | | | 3 | 3 | — | 9 | – | 1 | 3 | 4 | 23 | 28.1 |
| Normal WBC | | | 5 | 2 | 9 | 11 | 1 | 7 | — | 19 | 54 | 65.6 |
| *Lymphocytosis* | | | 6 | 3 | 11 | 11 | 1 | | — | 16 | 48 | 58.5 |
| Atypical lymphocytes | 1 | 2 | 6 | 3 | 11 | 6 | 1 | 9 | 14 | 18 | 71 | 86.6 |
| Heterophil positive | | 1 | | | 1 | 1 | – | 2 | 3 | — | 8 | 9.8 |
| Lymphadenopathy | | | | 3 | — | 1 | | 7 | 1 | 2 | 14 | 17.1 |
| Rash | | | | | — | — | | 4 | 2 | 1 | 7 | 8.5 |
| Pharyngitis | | | | | — | — | | 1 | 1 | 2 | 4 | 4.9 |
| Onset (in days) | | | 19-48 | 20-30 | 8-42 | 21-49 | 50 | 21-55 | 13-32 | 14-37 | | |
| Sex | | | | | | | | | | | | |
| Male | | | 5 | 2 | — | 6 | – | 3 | 8 | 8 | 32 | 39.0 |
| Female | | | 1 | 1 | — | 8 | 1 | 6 | 6 | 13 | 36 | 43.9 |
| Age | | | | | | | | | | | | |
| <20 yr | 1 | – | 1 | 3 | — | 7 | 1 | 9 | 6 | 10 | 38 | 46.3 |
| >20 yr | | | 5 | | — | 7 | – | – | 8 | 11 | 31 | 37.8 |
| Cardiac disease§ | | | | | | | | | | | | |
| CHD | 1 | | 3 | 3 | — | 11 | | 9 | 10 | 15 | 54 | 65.9 |
| AHD | | | 3 | | — | 1 | 1 | | 3 | 5 | 13 | 15.9 |
| Other | | | | | — | — | | | 1 | 1 | 2 | 2.4 |

*Numbers [illegible] data from this study.
†[illegible]
‡[illegible]
§[illegible]

eosinophil counts. Examination of bone marrow has also revealed eosinophilia on 2 occasions.[4,7] The precise reason for the elevated eosinophil counts cannot be given, but I have noted several cases of moderate eosinophilia after open-heart surgery in which the patients had neither postperfusion syndrome nor a history of allergy.[11] In other instances, examination of bone marrow has shown erythroid hyperplasia,[8] plasmacytosis, or an increase in reticulum cells,[4,7] but no diagnostic pattern was found in any case.

Hemoglobin, hematocrit, and total red blood cell counts were variable in this study, and, when low, showed stable levels during the acute phase of the postperfusion syndrome. The original decrease occurred in the immediate postoperative period, and one or two transfusions invariably corrected the hemoglobin values. The reticulocyte count was either normal or slightly increased but never exceeded 7 per cent. Wheeler and associates[4] reported similar findings, and direct antiglobulin tests on 2 patients were negative. Holswade and associates[6] did not consider anemia to be a feature of the postperfusion syndrome. On the other hand, Pirofsky[18] noted 7 cases of hemolytic anemia in the postoperative period in patients who had undergone aortic valve surgery, 4 of whom also developed febrile lymphocytic splenomegaly. Direct antiglobulin tests in these patients were positive. Although the association of hemolytic anemia in these 4 patients tends to suggest the contrary situation, anemia per se does not appear to be a component part of the postperfusion syndrome in view of the findings in the 82 cases reviewed here.

Serologic tests included heterophil agglutination titers, which were reported to be positive in 8 cases. Toxoplasma antibody tests have been uniformly negative.[4,6,8] Antistreptolysin O tests, when

performed[3,4] have been nondiagnostic and an antiheart antibody test performed in one case was negative.[7] Widal agglutination, lupus erythematosus, and direct antiglobulin tests performed in a few cases were negative.[3]

The etiology of the postperfusion syndrome remains unknown. The pump oxygenator has been eliminated as a cause since this illness developed in 2 patients in this study who had not been operated upon using the cardiopulmonary bypass technique and also in 2 cases reported by Bastin and associates[9] as well as in the 23 cases noted by Bergstrom and Dahlstrom.[18] (This latter group of patients was operated on for tuberculosis.)

There is good evidence that the syndrome is not due to bacterial or fungous septicemia, since hundreds of blood cultures in the 82 patients reported on have not demonstrated a single positive result. The likelihood that the illness is infectious in nature is strongly suggested by other data. Although many authors have noted a sporadic occurrence, 12 of the 21 cases of postperfusion syndrome presented here occurred between September and January, and there was also a very high incidence in 1959, despite a similar number of operations each year. Wheeler and associates,[3] Holswade and associates,[6] and Smith[8] found similar, apparently seasonal distributions in their cases. A viral etiology is suggested by the inclusion-like particles noted within the cells of the spleen and lymph nodes in the necropsied case reported here.

The postperfusion syndrome most closely resembles infectious mononucleosis (Table IV)[14,16] with fever, splenomegaly, and atypical lymphocytes. Other less common signs and symptoms noted in infectious mononucleosis are also seen in postperfusion syndrome, and these include pharyngitis, lymphadenopathy, skin rash, normal white blood cell count, hepatic chemical abnormalities, variable incubation time, and a generally benign course. The postperfusion syndrome appears to develop more commonly in patients with congenital heart disease than in those with acquired heart disease, although this may be a manifestation of the youth of the former.

The clinical and hematologic findings noted in most of these cases are not diagnostic of infectious mononucleosis, and perhaps the most compelling reason to consider postperfusion syndrome as a

*Table* IV. *Comparison of postperfusion syndrome to other symptomatic disease conditions*

| *Item* | *Infectious mononucleosis* | *Postperfusion syndrome* | *Acute infectious lymphocytosis* | *Serum sickness* |
|---|---|---|---|---|
| Age | Less than 30 usually | Less than 30 usually | Children | All ages |
| Sex | 3M:2F | ? | | |
| Onset | Delayed | Delayed | Delayed | Delayed |
| Fever | + | + | + | + |
| Lymph node enlargement | + | ± | ± | + |
| Splenomegaly | + | + | − | − |
| Hepatomegaly | ± | ± | − | − |
| Pharyngitis | + | − | ± | ± |
| Rash | ± | ± | ± | + |
| Leukocytosis | Moderate to normal | Usually normal | Marked | Moderate |
| Lymphocytosis | + | + | + | − |
| Neutropenia | + | + | + | + Early |
| Atypical lymphocytes | + | + | − | − |
| Heterophil | + | ± | − | − |
| Etiology | ? | ? | | Foreign protein |
| Course | Usually benign | Benign | Benign | Usually benign |
| Signs prolonged | + | + | − | ± |

+ = Usually present; ± = Variably present; − = Usually absent.

form of infectious mononucleosis is the positive heterophil agglutination titer reported in some of these cases. However, even a suggestive heterophil titer is not proof of infectious mononucleosis, since relatively high titers have been noted in other circumstances.[17] I am at present investigating the possibility of the formation of atypical or incomplete heterophil antibodies in some of these patients as the cause of negative agglutination titers. Also, blood from 2 patients is being cultured by Dr. Helene Schneider of Baptist Memorial Hospital, Memphis, Tennessee, who reports that she has developed a technique that renders a specific cytopathic effect in tissue culture with sera from patients with infectious mononucleosis.[18] Other possible etiologies that have been suggested are a leukocyte graft versus host reaction[6,1] and the activation of a latent endogenous virus by the stress of the operation. Dr. Wolf Zuelzer (of Children's Hospital, Detroit, Michigan) thinks that this latent endogenous virus might behave in a manner similar to that theorized for herpes simplex virus.

Differentiation of the postperfusion syndrome from other postoperative complications usually is not difficult. Postpericardiotomy syndrome (postcommissurotomy syndrome) has a delayed onset and may consist of paroxysmal attacks of fever, malaise, chest pain, and pleural and/or pericardial effusions.[4] The symptoms are usually controlled with aspirin or steroids, which are of uncertain benefit in postperfusion syndrome.[4,8] Usually no splenomegaly is present, and there is often a neutrophilic leukocytosis.

The postperfusion pulmonary congestion syndrome occurs in the immediate postoperative period and is characterized by fever, dyspnea, and cyanosis.[4,5] The peripheral blood picture is usually not compatible with postperfusion syndrome, and this cyanotic dyspneic state appears to be a serious complication which often results in the death of the patient.

Septicemia or endocarditis may mimic in many ways the postperfusion syndrome, but the clinical course and the blood culture studies have in my experience pointed out the true etiology in those cases which came to necropsy at a later date. Of the 4 such cases, 3 patients developed proved Candida septicemia, and the fourth patient had *Micrococcus albus* cultured from the blood ante mortem and from the diseased aortic valve at necropsy. In all cases the septicemia developed weeks after surgery, in that period during which most patients have developed postperfusion syndrome, and this fact suggests that blood cultures and other diagnostic tests should not be abandoned too quickly.

## Summary

Twenty-one cases of postperfusion syndrome are described; the illness consists of fever, splenomegaly, and atypical lymphocytes in the peripheral blood after cardiopulmonary bypass and occasionally after other operative procedures in which large quantities of blood are transfused. Infrequently the heterophil agglutination titer will be positive, as noted in cases reviewed from the literature. The illness, which is benign in its course, closely resembles infectious mononucleosis, although other agents may be responsible. Differentiation from other postoperative complications and possible etiology and pathogenesis are discussed.

I wish to express my thanks to Dr. J. R. McDonald, Dr. T. L. Jarkowski, and Dr. F. D. Dodrill and to all of the physicians who allowed me to use the records from their cases. I especially wish to thank Miss Isabelle Foster and Mrs. Doris Furcron *for their assistance in the laboratory work.*

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## Apex cardiography


*E Grey Dimond M D**
*Asaria Duenas M D*
*Alberto Benchimol M D*
*La Jolla Calif*


For the past several years we have studied the possible usefulness of apex cardiography We have described our results in a series of papers[1-11] In recent literature other workers have described their experiences[12-4] Hartmann[13] in particular stimulated our initial interest

**Technique**

We have now recorded several thousand apex cardiograms and although this figure is irrelevant the number is over ten thousand From this experience we can make these generalizations

*1* An apex cardiogram by our definition refers to a recording made at the *point of maximal impulse* with the patient in a left lateral position and in mid expiration

*2* If a right heart cardiogram is desired the patient is supine in mid expiration and the recording is made from the area of maximal pulsation which is identified by eye and hand

*3* Whether apex cardiogram or right heart cardiogram the pulsation is first visualized on an oscilloscope and the pickup piece is shifted slightly until a tracing demonstrating a clear O point (opening of the mitral or tricuspid valve) and a clear initial systolic lift (isometric contraction) is seen on the oscilloscope If these two physiologic events can be clearly discerned then the vibration is considered to be adequate for analysis and a recording is made Note this variable Although the point of maximal impulse identifies the location for application of the pickup still further adjustments of location are necessary by viewing the tracing on the oscilloscope until these two basic landmarks can be seen The pickup piece is applied quite firmly and is held in place by hand Respiration is suspended

The following additional variables must be considered

*A Size of pickup* The diameter of the funnel which comes into contact with the skin may vary from 2 to 5 cm depending upon the extensiveness of the precordial movement A sharply localized thrust may be analyzed with a small pickup a larger area of movement may require a pickup of larger diameter The timing of events is not varied by changing pickup however the contour especially the latter half of systole can be altered by this variable

*B The frequency range of the apex cardiogram* We have attempted to confine our studies to the frequency range which is undoubtedly below the hearing range specifically below 25 cycles per second


From the Institute for Cardiopulmonary Diseases, Scripps Clinic and Research Foundation La Jolla Calif


Supported in part from the National Institutes of Health Research Grant No 5 RO1 HE 07983 03 and Cardiovascular Training Grant No. 2 T1 HE 5313-04
Received for publication Nov 18 1965


*Address Scripps Clinic and Research Foundation 476 Prospect St La Jolla Calif

We have accomplished this by filtering out frequency variations above this range. There is no uniform agreement upon this subject however, and the term "apex cardiogram" is used by various workers to include vibrations of a higher spectrum.

*C Characteristics of the sensing device* We have used the Sanborn crystal microphone No 374 and the Schwarzer transducer Z101/37 and have found a quantitatively similar apex cardiogram. However, we have not performed the necessary analysis of each of these microphones and we do not know their response characteristics. Later in this paper we cite the correspondence from Eddleman, who has not found the frequency response of the Sanborn microphone to be linear (*infra vide*).

The obvious possibility that the apex cardiogram as described here is a synthesis not only of true cardiac events but also of nonspecific rotation of the heart and of resonance of the thoracic cage, all compounded by some digital dexterity on the part of the operator, makes this technique suspect. If the method is admitted to be a crude attempt to quantitate physiologic events, and if it is accepted that more refined instrumentation will come along, then there still is sufficient reason at the present to attract the clinician. There is also sufficient factual physiologic information to make this method of interest to the investigator.

The results with apex cardiography in recent years can be summarized as follows:

*1* The apex cardiogram faithfully records the onset of ventricular contraction and, when used in conjunction with the carotid trace and phonocardiogram, offers an indirect means of determining isometric contraction, ejection time, isometric relaxation, ventricular filling time, and the interval from the onset of atrial systole to the initiation of isometric contraction.[illegible]

*2* The apex cardiogram is a useful reference tracing and provides a time record of the *onset* of left ventricular filling and the *rate* of left ventricular filling, and therefore analysis of this phase of the apex cardiogram can be useful in the discrimination of mitral regurgitation from mitral stenosis.[illegible] The 2-OS interval can be determined in the absence of an opening snap by measuring the interval from the second heart sound to the O point.[illegible]

*3* The apex cardiogram records the precordial vibration associated with atrial contraction, and the recorded tracing is useful in quantitating the amplitude of this vibration. The clinical usefulness of this fact needs further study, however. Our own studies have indicated a considerable relationship between the presence of an abnormal left ventricle and a large atrial wave vibration. This relationship can be further defined as follows:

*A* A large atrial component is present in those conditions in which a thickened compensated left ventricle is present—aortic stenosis, subaortic obstructive disease, hypertensive cardiovascular disease, any nonspecific myocardiopathy.[illegible]

*B* A large atrial component is present in ischemic heart disease in the presence of an apparently compensated left ventricle of normal size. There seems to be a direct relationship between the severity of the ischemia and the amplitude of the atrial component. Exercise will exaggerate the amplitude of the atrial vibration, whereas nitroglycerin will result within minutes in a marked decrease or even disappearance of the atrial vibration.[illegible] Aging alone is not associated with this enlarged atrial component.[illegible]

*C* The large atrial vibration has some quantitative relationship to the level of the left ventricular end-diastolic pressure.[illegible]

*D* In a patient with ischemic heart disease and with a large atrial vibration and an elevated left ventricular end-diastolic pressure who clinically is *not* decompensated, acute digitalization will not alter the large "a" wave nor the elevated end-diastolic left ventricular pressure. The "a" wave does not decrease, and the left ventricular end-diastolic pressure does not decrease, yet immediately thereafter in the same patient sublingual nitroglycerin will decrease both the end-diastolic left ventricular pressure and the amplitude of the atrial wave. This observation has suggested to us that during angina pectoris there is an elevated left ventricular end-diastolic pressure, and that this elevated pressure does not represent one "usual" concept of left heart failure, but that instead we must consider an alternative to

heart failure. A loss of left ventricular compliance during ischemia has been suggested.[illegible]

*E*. In patients with ischemic heart disease in whom an elevated left ventricular end-diastolic pressure and a large atrial component in the apex cardiogram are recorded, not only nitroglycerin but also venous tourniquets will reduce to normal or near normal these two parameters. Furthermore, a tight abdominal binder (Kerr-Lagen belt) will cause this same alteration toward normal. These observations suggest that at least one of the effects of nitroglycerin is to decrease venous return.[illegible]

*F*. In some individuals with ischemic heart disease, smoking results in an increased atrial vibration, and venous tourniquets prevent this alteration. This observation suggests that one of the actions of smoking is to increase venous return.[illegible]

In summary, an increased atrial component to the apex cardiograms seems to be a constant sign of an abnormally functioning left ventricle. It is not diagnostic and cannot be used to separate conditions of hypertrophy, ischemia, or failure. However, from our present experience, the measurement of the amplitude of the atrial vibration expressed as a ratio of the total vibration at rest and after exercise seems to be a valuable screening procedure for identifying the presence of left ventricular disease. The difference in response of the atrial component to nitroglycerin and to digitalis may offer a means of separating primary ischemic disease from cardiac failure. Physical and pharmacologic agents may be appraised by suitable measurements.

*4*. The apex cardiogram in chronic left ventricular heart failure records prominent atrial waves and left ventricular filling waves (IV and III heart sounds). These alterations in the atrial wave can be returned toward normal by digitalis.[illegible]

*5*. In the presence of idiopathic hypertrophic subaortic stenosis the apex cardiogram frequently presents an abnormal systolic contour with an initial sharp rise, a fall off, and a second systolic dome—similar to the percussion and tidal waves of the arterial pulse. The apex cardiogram in idiopathic hypertrophic subaortic stenosis therefore frequently presents as a useful, almost diagnostic tracing with a prominent atrial wave, a sharp quick systolic rise, a fall off, and a rounded domed wave in later systole.[illegible] The site of the point of maximal impulse may be medial and superior in this condition, and it is this location to which we are referring.

*6*. In myocardial infarction, particularly if recent, but also in patients experiencing angina pectoris at the moment of the recording, a double systolic wave is recorded—a late systolic bulge, a sustained systolic wave.[illegible] Such a wave form in ischemic heart disease may represent a true myocardial aneurysm or may be but a temporary paradoxical movement due to the ischemia.[illegible]

*7*. A retracting impulse may be recorded in constrictive pericarditis and in association with pleuropericardial adhesions.[illegible]

The principal comments so far in this paper have related to the tracing obtained from the point of maximal impulse, thus the term *apex* cardiography. The same technique can be used to obtain a record of the movement of any area of the precordium. (In fact, identical equipment is used for recording the venous trace and the carotid trace in the neck.) We have restricted our analysis to the precordium and in addition to the left ventricular vibration we have recorded, in patients with *right* heart disease, adequate tracings from the xiphisternal junction and from the fifth intercostal space in the immediate parasternal line. Prominent right heart a waves are quite characteristic of pulmonary stenosis and pulmonary hypertension. The right heart cardiogram in rheumatic panvalvular disease has a close correlation to physiologic events. The possible usefulness of such recordings in congenital heart disease has been defined.[illegible]

### Related techniques

Although we have discussed only apex cardiography, other workers are accumulating similar and additional information using other techniques for recording precordial vibrations. These methods and their chief proponents are: (1) kinetocardiography (Eddleman, Harrison), (2) vibrocardiography (Agress), (3) impulse cardiog-

raphy (Mounsey) and (4) precordial accelerography (Rosa Luisada)

A brief résumé of the relationships and differences between these methods is given in Table I. The left hand column lists these methods and the accepted abbreviation of the terms. One method, vibrocardiography, records a broad sound spectrum; the other four record selectively the low frequency subaudible range.

We have recently corresponded with the individual workers and several current comments are significant. Luisada states that studies of the Altec Lansing microphone demonstrate a sharp drop in its response below 30 cycles per second and

*Table I Technical differences between methods*

| Method | Frequency range (cycles per sec) | Pick-up used | Characteristic transducer | Point of reference on precordium |
|---|---|---|---|---|
| Kinetocardiography (KCG) | D C –20 | Metal bellows and piezo-electric transducer (Statham P5A) | Displacement | ECG precordial lead leads (V to V) |
| Apex cardiography (ACG) | 0 1 20 | Schwarzer transducer or Sanborn crystal microphone 374 (with filter) | Displacement | Maximal apical impulse |
| Impulse cardiography | 1–10 | Photoconductive-cell (O R P 90 Mullard) | Displacement | Cardiac impulse in selected sites (apex left parasternal and right parasternal area) |
| Vibrocardiography (VBCG) | 30–500 | Altec Lansing capacitance microphone | Velocity and displacement | Fourth intercostal space cm from left sternal border |
| Precordial accelerography (PACT) | 5 75 | Electromagnetic transducer | Acceleration | Fourth intercostal space 1 3 cm to the left of left sternal border |

*Table II Range of published studies*

| Disease | Method | References |
|---|---|---|
| 1 Ischemic heart disease | KCG ACG VBCG PACT | 3 6 7 33-36 38 39 43-4 55 58 60 63 |
| 2 Mitral valve disease | KCG ACG Impulse cardiogram | 1 3 5 3 35 48 |
| 3 Aortic valve disease | KCG ACG | 3 8 13 29 3 5 64 65 |
| 4 Hypertrophic subaortic stenosis | ACG | 8 9 30 |
| 5 Idiopathic cardiomyopathy | ACG Impulse cardiogram | 8 29 31 48 |
| 6 Ventricular hypertrophy | KCG ACG Impulse cardiogram PACT | 1 3 7 9 11 13 15 20 3 5 6 8 3 3 4 44 46 48 55 58 64 65 |
| Congenital heart disease | KCG ACG Impulse cardiogram | 11 13 3 46-48 |
| 8 Reference tracing | ACG | 1 2 4 5 15 |
| 9 Me to th h effect of | | |
| Exercise | KCG ACG VBCG PACT | 3 6 15 33 35 39 43 44 60 63 |
| b Nitrites | KCG ACG | 2 3 6 7 33 35 39 44 |
| Digitalis | KCG | 40 41 |
| d Smoking | ACG | 7 |

that low frequency tracings with it are questionable. Furthermore correspondence from Eddleman states that he has found the kinetocardiography system to be fairly linear from D C to 20 cycles with a resonance at 80 cycles per second. He further found that the apex cardiogram has a marked *roll off in amplitude* response below one cycle per second with a marked phase shift both in the low frequency as well as in the upper ranges.[49]

Current correspondence from Mounsey[*] states that he has compared his impulse cardiography to the kinetocardiography metal bellows pick up using the same subject. Almost identical curves were obtained in relation to timing and direction of the wave. Differences between the kinetocardiography method and (the impulse method) are due to two main points (1) The amplification of our tracings both for the healthy subject and in heart disease is constant. Thus although the deflection of our tracings in health is small their amplitude can then be compared with that seen in the presence of ventricular hypertrophy where the patient shows clinically a large sustained outward lift. (2) The force applied to the chest wall by the instrument pressing upon it is probably greater in the case of the kinetocardiographic metal bellows than with our impulse cardiograph. We have measured the force exerted by the light springs in our instrument and found it is between 100 and 200 grammes over the range of displacement measured. Due to the stiffness of the metal bellows of kinetocardiography I imagine that especially with large movements of the chest wall the force exerted by the kinetocardiographic probe on the chest wall must be of greater order. Since by exerting force in the intercostal space one can presumably actually displace the heart backwards slightly this is another cause of minor differences between our two displacement records.

Agress[41] advised us that he has changed his nomenclature from the letter system to the numbering system with the anticipation that this would be more practical and would eliminate some of the confusion arising from association with ballistocardiography (see Fig 1).

Table II provides an index to the published studies with these various approaches.

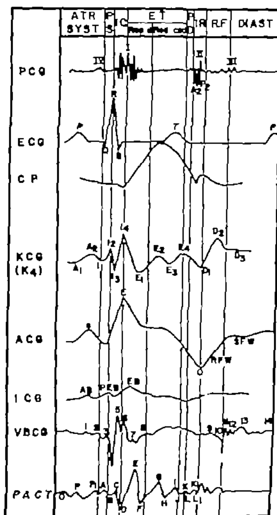



Fig 1 Correlation of the records obtained with the various techniques. See text

Fig 1 attempts to correlate the records obtained with these various techniques. The apparent dissimilarity is misleading instead note that all tracings document major vibrations synchronous with cardiac events.

## Summary

For the past several years we have studied the possible clinical usefulness of recording the low frequency precordial vibrations put in motion by the cardiac cycle. We have confined our analysis to the technique of apex cardiography. Our approach has been that of clinical empiricism

specifically we have prestated the clinical variable using standard disease patterns and then analyzed the apex cardiographic response to this variable Subsequently we altered pharmacologic and physical variables and again noted the apex cardiographic response

Simultaneously and in some instances earlier other investigators have also studied precordial vibrations using the same or different methods The consensus seems to indicate that there is clinically useful information to be gained by analysis of this low frequency spectrum It is important to appreciate this fact inasmuch as the diversity of instruments nomenclature and method may alarm and dissuade others from gaining experience in this field

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# Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Alan F Lyon

## Antianginal drugs

## Part VI Beta-adrenergic blocking agents

*Solomon Fisch M D* *

*Bronx N Y*

In order to explain the biologic differences between various sympathetic amines it has been hypothesized that there are two types of adrenergic or sympathetic tissue receptors These are called α and β adrenergic receptors These new designations replace the confusing old terms of excitatory and inhibitory sympathetic actions It should be emphasized that this is only a working hypothesis α Adrenergic receptors are responsible for vasoconstriction and for contraction of the uterus nictitating membranes pupillary muscles splenic capsule and pilomotor apparatus they also mediate relaxation of the intestine β Adrenergic receptors cause vasodilatation relaxation of the myometrium and bronchi and augmentation of the rate and force of contraction of the heart Epinephrine mediates the action of both receptors Norepinephrine and isoproterenol are virtually pure α and β adrenergic receptor stimulators respectively Antagonists to α adrenergic receptor action or α blockers include phentolamine (Regitine) piperoxan hydrochloride (Benodaine HCl) and phenoxybenzamine hydrochloride (Dibenzyline) β Blockers have been developed only recently They are being studied primarily because of their potential usefulness in cardiovascular therapy They appear to act by competitive inhibition of their respective catecholamines The first β blocker dichloroisoproterenol (DCI) bore structural similarity to isoproterenol It was discarded because it had too much sympathetic activity of its own Subsequently pronethalol and propranolol and several others which are in various stages of investigation were introduced Despite minor differences these compounds behave pharmacologically in similar fashion and will be discussed as a group with major emphasis on their cardiovascular effects

*Cardiovascular effects* Compounds suspected of having β adrenergic blocking ability are screened by their ability to block the cardiovascular effects of exogenous isoproterenol Compounds that do this have been considered to block the effects of endogenous β adrenergic stimulation as well

The exact role of the myocardial β adrenergic receptors and of the endogenous amines that presumably mediate their myocardial effects is unknown In resting normal men β blockers have no effect In hypertensive subjects at rest a modest lowering of cardiac output left ventricular work heart rate and brachial arterial pressure occurs In both groups *during or after exercise* the drugs reduce pulse blood pressure cardiac output and left ventricular work and increase heart size stroke volume and systolic ejection time There is a slight decrease in the velocity of contrac

Received for publication [illegible]

*Director Cardiac Therapy Research [illegible] Veterans Administration Hospital [illegible] Bronx N Y [illegible]

# Annotations

## Diuretic treatment of primary lymphedema

Primary lymphedema is an uncommon but by no means rare cause of peripheral edema. It occurs three times more commonly in women than in men and a family history of similar edema is obtained in some 20 per cent of patients. The etiology and pathology of this condition remained obscure until the introduction of lymphangiography demonstrated a basic defect in the lymphatic channels. The site of this defect lies in the main subcutaneous lymph trunks and may be one of three types. Aplasia of the lymph trunks is present in about 10 per cent of cases when no formed lymph trunks can be demonstrated. This is commonly associated with severe and progressive lymphedema which becomes clinically manifest in infancy. More commonly in some 75 per cent of affected subjects there is hypoplasia of the lymph trunks with abnormalities in both the size and the number of the lymphatics. Although also a congenital maldevelopment, this defect may not become apparent until adolescence or early adult life and in general has a relatively benign course. The lymphatic defect in the other 15 per cent of cases is one of varicose or dilated and tortuous lymph trunks with marked incompetence of these channels as evidenced by backward flow and lateral spread of dye on lymphangiography. This type of defect is commonly evident in infancy, is severe and progresses rapidly.

*The functional result of these defects is a failure* in the normal removal of particles of large molecular size from the interstitial spaces by the lymphatics. In particular the small quantities of plasma proteins which enter the interstitial spaces are not removed but accumulate. Their osmotic activity results in an increase in subcutaneous fluid and clinical edema. Studies of edema fluid have confirmed a high content of protein and investigations using I[131] albumin show defective removal of the labeled protein from lymphedematous limbs. This latter observation is in contrast to the increased removal of subcutaneously injected I[131] albumin in subjects with edema due to heart failure, hypoproteinemia or venous obstruction.

Clinically the typical patient with primary lymphedema is an adolescent girl or young woman with spontaneous edema *of one or both legs*. Initially there may be only slight painless pitting edema of the ankle, most evident in the evening and commonly worse in hot weather or before menstruation. The initial complaint is largely cosmetic but as the disease progresses the limbs become more swollen, heavy and burdensome. Secondary fibrosis in the subcutaneous tissue develops with or without recurrent attacks of cellulitis. Pitting no longer is possible and the swelling becomes more constant. In general, edema is greatest and its progression more rapid in patients with lymphatic aplasia or varicose lymphatics.

Diagnosis depends on exclusion of other systemic causes of edema, analysis of the protein content of the edema fluid (> 1.5 Gm. per cent) and lymphangiography.

Treatment of this condition in the past has been far from satisfactory. In advanced cases considerable benefit may be obtained from surgical treatment, but the need for this is a reminder of our inability to control the condition in its earlier stages before gross unsightliness and disability develop. Conservative management of lymphedema, which includes elevation of the limb and supportive bandaging, is singularly unsatisfactory. Although such therapy may be acceptable to patients with extensive and disabling edema, few subjects with mild swelling are prepared to follow this regimen. It is, however, in mild cases that treatment is possibly most necessary, for it has been suggested that failure to control the early accumulation of protein-rich interstitial fluid leads to recurrent infection and progressive fibrosis with irreversible changes in the subcutaneous tissues.

*In view of the success of modern diuretic therapy* in the management of patients with cardiac, renal and hypoproteinemic edema, it is not surprising that such therapy has been advocated for subjects with lymphedema. On theoretical grounds it might be expected that diuretic therapy would be of only limited value in a condition in which edema appears to result primarily from the local accumulation of osmotically active interstitial protein and not from the inappropriate renal retention of sodium and water as in cardiac, renal and hypoproteinemic edema. Early reports on the use of diuretics in this condition claimed that they were effective. However, few patients were studied and in the main these had advanced disease. Furthermore, no clear distinction was made between patients with primary lymphedema and those with venous insufficiency.

A more critical assessment of the place of diuretic therapy in this disorder has recently been carried out. In a carefully controlled study, 27 patients in whom primary lymphedema was diagnosed were included in a double-blind crossover trial. The design of the trial was such that the results [illegible]

were not affected by spontaneous changes in the lymphedema due to menstruation, climatic conditions or variable dietary habits. The response to therapy was evaluated both on the patient's symptoms and subjective assessment and on measurements of body weight and limb circumference and volume. The drug employed was chlorothiazide in a dose of 500 mg. twice daily for 5 days in 7. Each patient was studied for at least 28 weeks: 14 weeks on therapy and 14 weeks on placebo, with the order randomized.

This study showed great differences in the response to therapy, varying from nil to considerable in individual cases. Subjective improvement was claimed by 18 of the 25 patients who completed the trial, but corroborative objective evidence was lacking in 4. Among the 14 patients who improved there was considerable symptomatic and/or objective improvement in 5, moderate improvement in 2, and only marginal improvement in 7. An additional 3 patients with objective evidence of considerable reductions in edema did not admit to any symptomatic improvement. Overall, worth while improvement was deemed to have been achieved in 10 of 25 patients and was considerable in 8 of the 10. In no case could it be considered that the lymphedema was completely eliminated.

Follow up studies on these patients showed the improvement to be maintained for periods up to 8 months. A 3 month follow up of 13 patients who failed to improve during the trial period demonstrated only slight improvement in 3 patients during this more prolonged period on diuretic therapy.

A retrospective analysis of the results of this trial failed to reveal any clear-cut criteria by which to select patients likely to respond to diuretic therapy. Thus the presence or degree of improvement could not be clearly connected with the degree or duration of the condition, although there was some suggestion that more severely affected subjects responded more often and more markedly. No correlation could be demonstrated between the response to therapy and a history of premenstrual aggravation of the edema or premenstrual tension.

It was concluded that diuretic therapy could be of considerable benefit in certain patients with lymphedema. The dosage schedule employed was safe and devoid of side effects. No clear selection possible of patients likely to respond to treatment, and for this reason subjects should be given a 3 month trial period. Patients failing to respond to this program are unlikely to benefit from more prolonged treatment.

W. R. *Cattell*, M.D., M.R.C.P., M.R.C.P.E.
*Senior Lecturer in Medicine*
G. W. *Taylor*, M.S., F.R.C.S.
*Professor of Surgery*
*St. Bartholomew's Hospital*
*London, England*

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# Endocardial pacing

In 195[illegible] Zoll described a technique for [illegible] of pacing of the heart which employs [illegible] electrodes placed on the chest wall [illegible] electrical stimuli of [illegible] msec. duration at 25 to 150 v. [illegible] method of pacing, although it [illegible] patient w[illegible] in resuscitating and temporarily maintaining life [illegible] with Stokes-Adams attacks [illegible] systole. An alternate method [illegible] temporary pacing by the transvenous [illegible] Furman [illegible] and Robinson[illegible]

in 1958 using a unipolar electrode passed via a peripheral vein into the right ventricle temporary pacing was then possible with low voltages and without discomfort to the patient

Techniques suitable for long term pacing of the heart were developed independently by Chardack and colleagues[4] and Elmqvist and Senning[5] in 1960 which consisted of direct stimulation of the heart by electrodes implanted at thoracotomy and attached to buried abdominal pacemakers Reports of experience of long term pacing by epicardial electrodes with or without implanted pacemakers have now been published by many authors The principal disadvantage of epicardial pacing is the necessity for a thoracotomy in a group of patients largely in their sixth and seventh decades which often results in complications serious enough to consider alternative methods of pacing However Vorschulte and colleagues[n] and Hirsch and colleagues[14] have placed the epicardial electrode through an upper abdominal and lower sternum splitting incision and this technique has considerably lowered the morbidity of epicardial pacing [n,n]

Many patients who were considered to be too old or ill for thoracotomy or who refused operation *were treated by endocardial pacing using unipolar* or bipolar electrode catheters introduced via the jugular venous system or occasionally the cephalic vein It was thought that this method of pacing for long term treatment would prove to be unsatisfactory because the electrode position would be unstable and there might be complications such as septicemia embolism and myocardial perforation [13,14] Reports have now appeared however confirming the advantages of endocardial pacing for the long term treatment of heart block [17,n] The initial positioning of the electrode tip in the right ventricle particularly with a unipolar catheter is critical for maintenance of pacing and placement is greatly facilitated by using a high-definition image intensifier preferably with a field of 7 inches or more Bipolar electrode catheter pacing is technically easier since the position in the right ventricle is not so critical but these electrodes have not proved to be entirely satisfactory because of fractures of the wire [14,n] When the unipolar endocardial electrode is made the negative pole less power is required to pace the heart than with the bipolar electrode and this is an important consideration when the electrode is attached to an implanted pacemaker and lowers the possible risk of producing ventricular fibrillation but suffers from the disadvantage that the subcutaneous positive pole may occasionally cause troublesome local stimulation of skeletal muscle With bipolar electrode pacing the circuit is completed through the blood in the right ventricle and this results in the deposition of fibrin and the formation of thrombus by the negatively charged blood elements depositing on the positive pole which may result in a progressive rise in the threshold for pacing and the occurrence of pulmonary emboli With unipolar endocardial pacing the formation of thrombus has never been a problem and anticoagulant therapy is unnecessary [n,n] Perforation of the heart by the C50 No 5 endocardial electrode has occasionally occurred usually at the time of insertion of the electrode catheter or as a late complication when attached to an *external* pacemaker and the larger and more rigid bipolar catheters may be worse in this respect Fortunately perforation of the heart by an endocardial electrode has not so far resulted in serious sequelae and it is usually possible to continue pacing after the endocardial electrode has been repositioned [n]

When the endocardial electrode is exteriorized in the neck or anterior chest wall and attached to an *external* pacemaker the chief complications are the relative ease with which a patient can accidentally pull the electrode out of position and the risk of septicemia from the small area of infection which occurs around the electrode's site of exit in the skin [n] Septicemia is particularly liable to occur if the electrode has to be repositioned in the presence of local infection or in the presence of rheumatic or congenital heart disease (a contraindication to endocardial pacing if an *external* pacemaker is used) If septicemia does occur cure with antibiotics is only likely to be achieved if the endocardial *electrode is removed* [n] Nevertheless despite these hazards successful endocardial pacing with an *external* pacemaker has been reported in patients for as long as 3 years [15,n]

A logical development in the technique of endocardial pacing was implantation of the pacemaker [n] thereby reducing the risks of septicemia and accidental displacement of the electrode from a satisfactory pacing position in the right ventricle and avoiding the risk of bacterial endocarditis in patients with rheumatic or congenital heart disease A few months after installation of an endocardial system using the unipolar C50 No 5 electrode with an *implanted* pacemaker in the axilla some electrodes fractured resulting in intermittent pacing a complication not encountered with unipolar endocardial pacing and an *external* pacemaker [n,n] The stress fracture occurred in the electrode at the point at which the catheter was inserted into the jugular venous system and was due to angulation of the electrode catheter in the neck during movements of the shoulder which moved the *implanted* pacemaker in the axilla It is probably better to implant the pacemaker unit in the anterior chest wall thereby avoiding the mechanical stress on the C50 No 5 electrode catheter which occurs with movement of the shoulder when the unit is implanted in the axilla Implantation of the unit in the anterior chest wall is usually possible in most women but not always in thin men because of the size and shape of the pacemaker unit With the thin patient a coiled stainless steel link between the pacemaker unit implanted in the axilla and the C50 No 5 electrode catheter in the anterior chest wall may avoid stress fractures[1] An alternative is to use the *external* pacemaker with the endocardial electrode catheter having a long subcutaneous course on the anterior chest wall [n] Recently more flexible electrode catheters have been developed[n,n] for use with *implanted* pacemakers but they are more difficult to introduce into the right ventricle via the

C50 CH C52 1 Catheter Corporation CT [illegible]

jugular venous system and the results of their long term use have not yet been reported

Abrams[8] has adapted an induction system of pacing to an endocardial electrode and this is proving to be satisfactory. The secondary coil is attached to a short length of a C50 No 5 electrode catheter and buried in the anterior chest wall. Because of the location of the coil and attached electrode catheter very little movement occurs in the electrode on movement of the shoulder joint and stress fractures have not occurred during 15 months of experience in 16 patients. This method of endocardial pacing combines the ease of servicing of the pacemaker unit which is possible with an *external* pacemaker and the low rate of sepsis and stability of the endocardial electrode expected with an *implanted* pacemaker.

Endocardial pacing has proved to be a valuable addition to the short term and long term management of heart block. The use of a unipolar endocardial electrode requires considerable experience for satisfactory placement and until experience has accumulated poor results may be obtained. For this reason the bipolar system may prove to be preferable when only the occasional patient is to be treated since its placement is less critical.

The main problem of maintenance of satisfactory pacing with implanted pacemakers is the production of a reliable pacemaker unit. Recently Dack[25] reviewed pacemaker failure and it appeared that most commercially available units have a high incidence of component or battery failure. Unless tremendous attention to detail and very careful checking of components such as transistors and batteries are carried out at every stage of manufacture of pacemaker units a proportion of all units will continue to fail prematurely.

*A M Harris M B B S M R C P*
*Cardiac Department*
*St George's Hospital*
*London S W 1 England*

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# Atrioventricular and intraventricular conduction defects after nonpenetrating trauma

Atrioventricular and intraventricular conduction defects are not frequently reported following nonpenetrating bodily trauma. We were able to find 21 reported cases of the former and 14 of the latter condition. Atrioventricular conduction disturbances consisted of various degrees of A-V block, from prolonged P-R to complete heart block; they occurred either as a transient or as a permanent phenomenon. Intraventricular conduction defects also occurred both transiently and permanently.

A review of the literature shows that nearly two thirds of the cases of A-V block were described from 1912 to 1938; the remainder were observed from 1939 to 1964, despite the enormously increased number of traumatized patients encountered in these last years. Moreover, the exact role of trauma is difficult to ascertain in many published cases. Therefore, it is the purpose of the present paper to review criteria for establishing causal relationship of trauma to atrioventricular and intraventricular conduction defects.

*Heart and lungs before trauma.* In determining the causal role of trauma it would be ideal if heart studies could be obtained before and after injury. Unfortunately, this is often impossible, and the past cardiac status of the patient must be determined by careful direct questioning. (It is odd that in all reported cases of traumatic atrioventricular and intraventricular block no electrocardiogram had been recorded before trauma.) Now, for instance, it is well known that complete congenital heart block, unassociated with other important cardiac malformations, not only may be completely asymptomatic but also may not be diagnosed accurately during a medical visit. This condition is therefore very difficult to exclude in a young patient who sustains light trauma and has a very good tolerance of heart block in the years following trauma; such were the outstanding features of 2 reported cases of traumatic complete heart block. The congenital or acquired complete heart block existing before the occurrence of trauma is also not easily ruled out when the patient is middle aged or old. Fenton and associates reported that in some adult patients in whom heart block was discovered on routine examination no symptoms had been present previously. The presence of minor degrees of A-V conduction defect or of complete right and left bundle branch block in a certain percentage of a large healthy population furthermore points up the importance of electrocardiographic examination prior to trauma.

It has been stated that a diseased heart is more susceptible to traumatic injury than is a normal heart. In such an event, trauma may be the precipitating factor of cardiac disability. A pathologic cardiac process was evident in 4 reported cases in which trauma was, with the greatest probability, the trigger mechanism of A-V block. The presence of previous diseases capable of producing myocardial impairment was revealed by the past history in 3 other cases. Gore reported warns that a latent subclinical heart disease may be a source of error in attributing post-traumatic symptoms and signs to trauma itself. Unfortunately, no criteria exist to prevent diagnostic error in such cases. This is particularly true for conduction defects; cases are reported of patients in whom death ensued within a few hours after repeated Adams-Stokes attacks and in whom the clinical and electrocardiographic findings had been normal just before the terminal illness despite the complete destruction of the conduction system found at autopsy.

*Traumatic pathology of the conduction system.* Although a disturbance in the intrinsic nervous mechanism of the heart has been blamed to be responsible for the transient appearance of an A-V block after trauma, hemorrhages and laceration at the conduction system level are the more commonly postulated cardiac lesions in cases of permanent atrioventricular and intraventricular block. Nevertheless, the following clinical and experimental data stress that only with great difficulty can a healthy conduction system be injured sufficiently to produce permanent atrioventricular and intraventricular conduction defects.

For instance, all reported cases of isolated traumatic rupture of the interventricular septum have been reviewed by one of us; only 1 case out of 20 in which clinical or electrocardiographic records were available was complicated by complete heart block. Disturbances of A-V conduction were absent also when the rupture was extensive, located high up in the interventricular septum, and surrounded by extensive myocardial hemorrhage. In of 12 patients in whom an electrocardiogram was recorded showed intraventricular conduction defect: 4 had right bundle branch block, and 1 had left bundle branch block. In them, rupture was located in the middle and upper portion of the septum. Surgical repair of cardiac septal defects represents another situation in which injury occurs in the immediate proximity of the conduction system. In such an event heart block appears only in about 10 per cent of the cases and is transient in 70 per cent of them. Sometimes only right bundle branch block is evident. In spite of the finding of large areas of hemorrhage and infarction of the common bundle and both bundle branches on histologic examination.

Experimental findings are in accord with clinical data. In 1937 Schlomka found that trauma to the heart induced A-V conduction defects in only 17 of 86 rabbits which had been struck upon the chest, and he observed no permanent disturbance of A-V

conduction In dogs struck on the chest by heavy hammer blows changes in atrioventricular and intraventricular conduction tended to be transient unless the insults were repeated Pathologic evidence of myocardial injury (consisting mainly of subendocardial or subepicardial hemorrhages) was surprisingly small and in some cases edema of the myocardial fiber of the conduction system was postulated[18] It has also been demonstrated in dogs that the left upper part of the endocardial surface of the interventricular septum may be deeply cut and extensively lacerated without producing a permanent left bundle branch block[24]

*Conclusions* Basic criteria to be used in assessing traumatic etiology of heart block can be summarized thus youthful age of the patient absence of pre-existing heart diseases or conduction defects great magnitude of the injuring force electrocardiographic findings suggestive of myocardial involvement (abnormalities of both the QRS and the T waves) associated traumatic heart lesions (e interventricular septal defect or rupture of the aortic valve) absence of a long latent period between the time of injury and the discovery of block

Three reported cases of traumatic A V block, 10 cases of right and 2 cases of left bundle branch block satisfy most or all of these criteria and can therefore be considered to be of proved traumatic etiology The incidence of each type of conduction defect within this group might not be casual but related to the anatomic architecture of the conduction system which accounts for easier stretching and interruption of the right bundle than of the left or of the common bundle In other reported cases traumatic etiology must in our opinion be considered to be either possible or probable but not proved Two cases cannot be taken into consideration since the clinical findings were not sufficient to assess the presence of heart block

A critical attitude toward traumatic disturbances of atrioventricular and intraventricular conduction defects seems therefore to be necessary although we acknowledge that there are always important exceptions to any general rule for instance the large magnitude of the injuring force that we set up as a basic criterion may not be indispensable since a relatively small force applied under ideal circumstances can injure a particular organ This may apply as well to the conduction system

*Alberto Dolara M D*
*Lucio P M D*
*Electrocardiographic Service*
*Ospedale of S M Nuova*
*Florence Italy*

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# On the role of hydralazine in renal hemodynamics and secretion of renin

It ha been h wn in the p t by arious investigators that hydralazine is a un que drug in increasing renal blood flow Ex ept for pyrogen [1] n rmally no other agent has been found to have such specific effect upon the renal circulation

Recently it was ol erv d n the rat that the intr en us administration f h dralazine decreases the concentration of sodium and incre se the electrical re tance in the renal medulla without any ignifi ant alteration in other parameter in the rtex [2] In view of the fact that fter hydralazine the glomerular filtr tion rate remains unchang d these medullary chan es were attributed to an augmentati n f medullary bl od fl w This a sumption was made on the theory th t changes in the medullary c ncentrat on of sodium are inversely related to alterat ons in the medullary bl od flow (countercurrent d ffusion exchange mech ni m) [3]

Most recently it has bee reported that after alterat ons in the renal hemodynamics by renal artery st nosis man or by coarctation of the thoracic a rta in the dog [4] a marked increase in venous pla ma renin activity is observed after intravenous injection of hydralazine by using a rat [5] assay Most interesting is the ob ervation that i the ca of unilateral renal artery stenosis after hydralazine an incre in renin activity is not d only in the renal venous plasma of the affect d side [6] Another important find ng is that renin tivity is not altered after injection of pentolinium reserpine or the beta adrenergic blocking agent pronethalol [4] This suggests that the action f hydralazine in increasing the secret on of renin is unique and is probably not mediated by a neurogenic or humoral mechanism

Taking nto con ideration ur wn work and the observations f others [2-4] the following postulat with reg rd to the role f hy dralazine on renal hemodynamics and the secretion of renin is m de It is w ll known th t the m t bulk f granules secreting renin is l cated in the peripher l portions of the cortex nd that granularity i le prominent toward the juxt m dullary junct n and absent in the medulla N rmally afte hydralazine n increase in total renal bl od flow occurs Our d t imply indirectly the pos ibility that this increase

n flow is more prominent in the medulla than in the cortex. Perhaps because of autoregulation which operates mainly in the cortex[14] the cortex copes with the situation and thus cortical blood flow remains unchanged. Under abnormal conditions, however, particularly when renal artery stenosis is present, the autoregulating mechanism of the cortex may be defective because of the presumably existing reduction in perfusion pressure and the renal vasodepressor effect of hydralazine. Hence a relative increase in medullary blood flow after hydralazine could mean a redistribution of blood from cortex to medulla and a relative cortical ischemia which in turn might result in underdistention of the stretch receptors of the afferent arterioles; this would account for more granularity of the cells and an increased secretion of renin.

In summary, it is suggested that under the circumstances of reduced intrarenal perfusion pressure or diminished renal blood flow as a consequence of renal artery stenosis or coarctation of the thoracic aorta, an increased medullary blood flow after the administration of hydralazine could further alter the intrarenal hemodynamics and lead to an increase in the secretion and activity of renin.

*Ignatius J. Voudoukis, M.D.*
*Division of Hypertension*
*Henry Ford Hospital*
*Detroit, Mich. 48202*

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# Book reviews

ELECTROLYTES AND CARDIOVASCULAR DISEASES Vol. II Clinical Aspects. *Edited by Eors Bajusz* University of Montreal. Baltimore, 1966. The Williams & Wilkins Co. 442 pages. Price $16.

Volume II of this series contains short papers by many authors writing on other aspects of electrolyte metabolism in cardiovascular diseases. This volume is divided into two parts. Part A is concerned with pathologic and physiologic problems and Part B is concerned with prevention and therapy. Part A presents discussions of primary myocardial disease, potassium depletion, potassium and the electrocardiogram, the shift of the S-T segment, and arterial hypertension. In Part B the discussions are of potassium treatment, the use of electrolytes in cardiopathies and in the treatment of myocardial infarction, potassium and the A-V node, and the use of Mg and K in cardiac therapy. Prevention is neglected to a great extent. On the whole this volume is good one and the two *volumes together provide a fine source of information on electrolytes and* cardiovascular diseases. Both volumes should prove to be very useful to internists, cardiologists and physiologists and will provide the undergraduate students with interesting and useful information. Experts in this field will find the ideas to be provocative and will not agree with all thought expressed but will find interesting problems that need investigation.

Like the first volume, the second is a good one.

INTRAVASCULAR CATHETERIZATION. Edited by Henry A. Zimmerman, M.D., B.S., St. Vincent Charity Hospital, Cleveland, Ohio, ed. 2. Springfield, Ill., 1966. Charles C Thomas. 1297 pages. Price $39.50.

This book, edited by Dr. Zimmerman with 26 contributors, is a very good edition. The first edition met with considerable success. This edition was expanded and is quite comprehensive. The beginner as well as the experienced cardiologist will find the presentation not only useful but well written and the text clearly illustrated. There are chapters on technique, method of analysis of curves, applications of method in diagnosis, interpretation of data, congenital and acquired heart disease, pulmonary circulation, cerebral blood flow, coronary circulation, and other. The techniques of selective angiocardiography and cineangiocardiography are discussed very well. *The bibliographies* are good and there are good subject indexes. This book, now over a thousand pages in length, is encyclopedic *in nature*. It is highly recommended as a reference source as well as a book worth owning on the subject of cardiac catheterization.

THE HEART. Edited by J. Willis Hurst, M.D., and R. *Bruce Logue*, M.D. New York, 1966. *Blakiston* Division, McGraw-Hill Book Company. 1255 pages. Price $25.

Hurst and Logue have edited a good book on cardiology with 66 contributors representing various fields. The book is similar in design to Cecil and Loeb's textbook of medicine. Like Cecil and Loeb's, this book tends to be brief but at the same time includes a thorough coverage of major problems of cardiology, including the peripheral vessels. However, the section on the peripheral vessels not only is inadequately presented but also gives a disproportionate amount of emphasis to the surgical aspect. The presentations are clear, the book is profusely illustrated, and the bibliographies appended to each section are good. With this very fine textbook of cardiology, Hurst and Logue have made an excellent contribution to the field of medicine. Students, general practitioners, internists and cardiologists should find this book to be very useful and will want to own a copy.

## Books received

CARING FOR THE AGED. By Bertram B. Moss with *Fraser Kent*. New York, 1966. Doubleday & Co. Inc. 372 pages. Price $4.95.

FUNDAMENTALS OF HYPERBARIC MEDICINE. Publication No. 1298 prepared by the Committee on Hyperbaric Oxygenation with support of the National Institutes of Health, Public Health Service, and the Office of the Surgeon General, Department of the Army. Washington, D. C., 1966. National Academy of Sciences, National Research Council. 178 pages. Price $6.

MATHEMATICS IN MEDICINE AND THE LIFE SCIENCES. By George R. Stibitz. Chicago, 1966. Year Book Medical Publisher, Inc. 391 pages. Price $12.50.

MODERN TREATMENT. Vol. 3, No. 2, March 1966. Treatment of Neuromuscular Disorders. By Frank M. Howard. *B.* Treatment of Hypoglycemia. By Burt R. B. Bell. New York, 1966. Hoeber Medical Division, Harper and Row. 1,500 pages per year. Price $16 per year.

## Charles C Wolferth

Dr Charles C Wolferth died at the hospital of the University of Pennsylvania on Dec 26 1965 three hours after he had correctly recognized the initial symptoms of aortic dissection In the seventy eighth year of his vigorous life he was fully active in practice Within the year he had shared the platform with Dr Francis C Wood in conducting the weekly seminars of the Department of Medicine Two weeks before his death he had lectured in his capacity as Emeritus Professor to the third year class on angina pectoris He was the moderator of the weekly conference of the Cardiac Section and his daily private rounds continued to be a prime educational experience for students and house officers

Dr Wolferth was born in 1887 at Wolferth Station New Jersey He worked on his father s farm in his youth and subsequently attended Princeton University He was on the varsity football and swimming teams and was elected to Phi Beta Kappa en route to his bachelor s degree in 1908 After transferring to the University of Pennsylvania for medical training he continued to play varsity football and to attain scholastic honors He was president of his class when he received the degree of M D in 1912 His internship was served at the Hospital of the University of Pennsylvania (1912 1914) followed by a residency in Pathology (1914 1916) He was then appointed as the first Chief Medical Resident at the University Hospital (1916-1917) After this he entered the military services and served in France as Chief of the Medical Service of Base Hospital No 31 stationed at Contrexéville in Lorraine At the termination of hostilities and prior to his returning to the United States Major Wolferth attended several of the newly formed hospital cardiac clinics in London and he was assigned for a time to the British Military Heart Hospital under the professional direction of Sir Thomas Lewis Dr Wolferth was one of several American graduates of that institution who returned to his university to organize a cardiac subspecialty group within the department of medicine At the University of Pennsylvania the Cardiac Section was developed by Dr Wolferth to investigate observe and report that which would contribute to medical knowledge in the cardiovascular field He was the Director of the Cardiac Section and also



Charles C Wolferth 1887 1965

Director of its research arm the Edward B Robinette Foundation for Cardiovascular Research until his official academic retirement in 1952 In actuality he never did retire from any of his professional interests and activities

Dr Wolferth's name appeared on 140 publications over a period of 47 years Many of his close professional associates collaborated with him on these papers including Drs T M McMillan Alfred Stengel T G Miller T FitzHugh J Edeiken S Bellet E Rose F D Murphy J J Sayen W F Sheldon A M Sellers A G Hills H F Zinsser C W Crumpton and M M Laverey The subject matter ranged broadly across the cardiovascular field quinidine and digitalis arrhythmias experimental myocardial ischemia hypoxia heart muscle lesions and the electrocardiogram angina and gall bladder disease and angina relief by thyroid depression are examples Many of these papers continue to be widely quoted but he will be best remembered for his outstanding contributions in auscultation electrocardiography and adrenalectomy for hypertension

Fourteen references are directly concerned with the mechanisms responsible for heart sounds Much of this work was undertaken in close collaboration with Dr Alexander Margolies They utilized sound recording techniques which were advanced in design for the time combined with roentgenkymography arterial and venous pulse recording and electrocardiography in the study of the factors influencing the intensity of the first heart sound and of the mechanisms of gallop rhythm opening snap sound and systolic clicks Their observations contributed greatly to the present understanding of cardiac auscultatory phenomena

Throughout his professional life Dr Wolferth was greatly interested in the theory and practice of electrocardiography A paper entitled The Electrocardiographic Diagnosis of Coronary Occlusion by the Use of Chest Lead by C C Wolferth and F C Wood was published in the *American Journal of Medical Sciences* in January 1932 Although chest lead had been employed in isolated instances for decades especially in the study of arrhythmias this was the first demonstration of the tremendous advantage of precordial electrode placement in the diagnosis of myocardial infarction It led to the utilization of chest leads as a standard clinical procedure within a very short time Another paper entitled The Mechanism of Production of Short P R Intervals and Prolonged QRS Complexes in Patients with Presumably Undamaged Hearts Hypothesis of an Accessory Pathway of Auriculoventricular Conduction (Bundle of Kent) also by C C Wolferth and F C Wood offered the concept of accelerated A V conduction in the explanation for this curious disorder This memorable publication proposing an alternative to the atypical conduction block concept appeared in the AMERICAN HEART JOURNAL in 1933 Ten years later Wood Wolferth and Geckler demonstrated an accessory atrioventricular muscular connection in the heart of a subject who had had in life the short P R interval syndrome

In 1949 Green's report of subtotal adrenalectomy in a hypertensive diabetic patient led Dr Wolferth to initiate a major program Adrenalectomy with and without sympathectomy was performed in 184 severely hypertensive patients Dr H A Zintel performed most of the surgical procedures Dr W A Jeffers Dr A G Hills and Dr F D W Lukens collaborated with Dr Wolferth in the intensive study of these patients which continues under the direction of Dr A M Sellers Adrenalectomy proved to be an effective therapy for severe hypertension at a time when alternative therapy was poor None of the patients who were operated upon subsequently developed congestive failure an observation of significance in relating adrenal function to congestive failure The 84 survivors continue to be a source of great investigative interest Dr Wolferth was the author or co author of 27 of the 81 publications that have derived from this clinical and experimental study of by far the largest group of patients subjected to adrenalectomy

In 1922 Dr Wolferth married Mary Beatrice Comber who predeceased him A son Dr C C Wolferth Jr is Clinical Associate Professor of Surgery at Hahnemann Medical College Two daughters of

that marriage also survive. In 1950 Dr. Wolferth married Dr. Mary Lavezey, Chief Cardiologist of the Chestnut Hill Hospital in Philadelphia.

Dr. Wolferth will long be remembered for his outstanding contributions to medical science and his remarkable skill as a physician and teacher. A less tangible but equally important memorial is in the hearts and minds of the many physicians who profited mightily from his wisdom and guidance.

*Calvin F. Kay, M.D.*
*Hospital of the University of Pennsylvania*
*Philadelphia, Pa.*

American Heart Journal

*August 1966 Volume 72 Number 2*

# Editorial

## Observations on the vascular anatomy of the pituitary gland and its importance in pituitary function

*Peter M. Daniel, D.M., D.Sc., F.R.C.P.*
*London, England*
*Marjorie M. L. Prichard, M.A., D.Phil.**
*Oxford, England*

It has been known for a considerable time that the anterior lobe of the pituitary gland (hypophysis cerebri) produces a number of specific hormones, but the means by which the production and release of these hormones are controlled was for long obscure. There was no convincing evidence that the cells of the anterior lobe were innervated, and yet there were strong indications that the release of most of these hormones was under hypothalamic control.[1,2] In recent years it has become increasingly apparent that the pathway through which this hypothalamic control is exercised must be that formed by the hypothalamo-hypophysial nerve tract and the system of hypophysial portal vessels. Some knowledge of the detailed anatomy of this unique neurovascular complex is essential, therefore, if one is to understand the means by which the central nervous system exerts its profound influence on the functions of the anterior pituitary. Our own studies of the pituitary have been largely concerned with its circulation and thus with the vascular component of the hypothalamo-hypophysial pathway. In the following account we review briefly some of the findings which we have obtained in both anatomic and functional studies which seem to be of special interest because of their physiologic or pathologic implications. The observations were made on the glands of human subjects, monkeys, sheep, goats, and rats. More detailed accounts with illustrations will be found in our other papers.

The pituitary gland is made up of three readily identifiable parts: the anterior lobe, which is composed of epithelial cells of characteristic secreting type; the posterior lobe, which consists of nervous tissue; and the stalk, which links these two lobes with the hypothalamic region of the brain. The stalk consists of a tract of nervous tissue leading to the posterior lobe, surrounded by a thin cuff of epithelial cells which forms an extension of

From the Department of Neuropathology, Institute of Psychiatry, Maudsley Hospital, London, England, and the Nuffield Institute for Medical Research, University of Oxford, Oxford, England.
Received for publication Oct. 18, 1965.
*Address: The Nuffield Institute for Medical Research, University of Oxford, 43 Woodstock Road, Oxford, England.

the anterior lobe. (In most species a third lobe, pars intermedia, composed of epithelial cells different from those of the anterior lobe, is interposed between the anterior and posterior lobes, but this is not distinguishable in the human pituitary.)

The posterior lobe has a conventional arterial blood supply obtained from the inferior hypophyseal arteries. The anterior lobe, however, is not supplied directly by any artery, but receives only portal venous blood, that is to say, blood which has already passed through a first capillary bed (Fig. 1). In man an anastomotic artery, the artery of the trabecula, which connects the superior and inferior hypophyseal arterial systems, passes through the anterior lobe but does not supply the epithelial cells.[3] (Some workers[4] believe that the human anterior pituitary is supplied by a few arterial twigs, but in our view such an arterial supply, when it exists at all, is so small as to be insignificant. In the rabbit, however, there is a fundamental difference from other species in that the anterior lobe has a substantial arterial, as well as a portal venous, blood supply.)

The portal blood is delivered to the anterior lobe by a number of individual portal vessels, and these vessels form two distinct groups, the long and the short portal vessels.[7,8] The *long* portal vessels are those which run down the pituitary stalk, but the *short* portal vessels lie below the level of the free part of the stalk (Fig. 1). On entering the anterior lobe the portal vessels of both groups break up to form the second capillary bed of the portal system, the sinusoids of this lobe. In these freely anastomosing sinusoids the portal blood is carried past the parenchymal cells and finally, laden with hormones released by these cells, is discharged through short venules at the surface of the anterior lobe into the venous sinuses which surround the pituitary. The venous drainage of the stalk is entirely by way of the

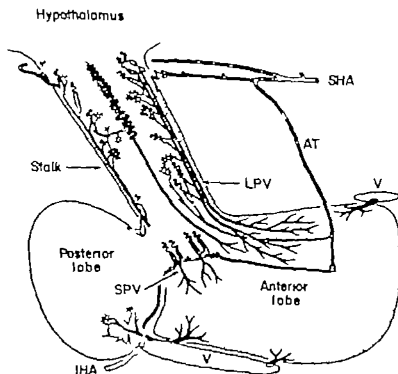



Fig. 1. Diagram of the human pituitary gland in the sagittal plane showing the main features of its blood supply referred to in the text. Glandular tissue stippled, neural tissue white. *LPV* Long portal vessels. *SPV* Short portal vessel. *IHA* Inferior hypophysial artery. *SHA* Superior hypophysial artery. *AT* Artery of the trabecula. *V* Venous sinuses adjacent to pituitary.

portal vessels there being no outflow into systemic veins

The primary capillary beds which feed the two groups of portal vessels both lie in the neural portion of the gland but at different levels The long portal vessels drain a capillary bed lying in the stalk itself whereas the short portal vessels drain a bed situated lower down The vessels which make up these primary capillary bed are of characteristic form being looped and convoluted with varying degrees of complexity some of those in the stalk being of a particularly striking pattern [7 8] The capillary bed in the stalk which feeds the long portal vessels is supplied by the superior hypophysial arteries whereas the bed which drains into the short portal vessels is supplied from the inferior hypophysial arterial system although in man it also receives some blood (via the artery of the trabecula) from the superior hypophysial arterial system

Although the anterior lobe of the pituitary resembles the liver in having a portal circulation it is worth pointing out that some of the well known features of the vascular arrangements and general structure of the liver are not present in the anterior pituitary For example in the latter there is nothing comparable to the contribution of arterial blood which is distributed to all parts of the liver by the hepatic artery Furthermore whereas in the liver the sinusoids and cords of parenchymal cells are arranged in countless small self contained units or lobules of uniform size each of which has its own individual afferent and efferent vessels i e small twigs of the widespread trees formed by the portal and hepatic veins [10] the anterior lobe of the pituitary has no lobular arrangement and nothing even on a small scale that resembles the intraglandular ramifications of the liver's afferent and efferent veins The whole anterior lobe consists of a single structural unit composed of a continuous network of freely anastomosing sinusoids lined by parenchymal cells and it is this network as a whole that is provided with afferent and efferent vessels Thus whereas in the liver an individual parenchymal cell whatever its position in the organ is never farther from a portal vessel than half the width of a lobule i e less than one millimeter in the anterior pituitary the distance between an individual cell and a portal vessel varies from a few micra to several millimeters depending on whether the cell adjoins a sinusoid at the proximal or the distal end of the entire network This varying distance implies a difference in the content of the blood bathing the parenchymal cells in different parts of the anterior lobe a fact which may well be of significance in regard to the functional activity of the individual cells

The existence of the *long* portal vessels *of the pituitary some of which are visible* to the naked eye on the surface of the stalk has been known since 1930 when they were first described by Popa and Fielding [11] who believed however that they carried blood up the stalk from the pituitary to the hypothalamus[1] since that time direct observations in living animals have shown that the blood in these vessels flows in the opposite direction namely down the stalk to the pituitary [12 13] The *short* portal vessels first described[7] in 1954 are less conspicuous than their long counterparts since except in the rat [8] they lie deep within the body of the gland Each group of portal vessels the long and the short has its own territory of supply in the anterior lobe and these territories are very clearly seen in glands examined a few days after transection of the pituitary stalk an operation which severs the long portal vessels but does not interfere with the circulation through the short portal vessels (see Fig 1) Such glands show a massive area of necrosis in the central and ventral parts of the anterior lobe [4] and this infarct demonstrates the very large territory which is *dependent for its supply of blood* on the long portal vessels e g up to 90 per cent of the lobe in man [17] Similarly the regular survival of small areas along the dorsal border of the lobe shows that these areas are supplied by the short portal vessels

However not only do the two groups of portal vessels each have their own territories of supply but the distribution of even individual portal vessels appears to be strictly circumscribed For if a very *small lesion* is made in the stalk *and only*

one or two of the long portal vessels, e.g., a few on one side, are cut or occluded, a small ipsilateral infarct regularly develops in the anterior lobe.[18,19] This shows that the territory supplied by a particular portal vessel receives little or no blood from the portal vessels which supply adjacent areas. It seems to be clear, therefore, that in spite of the free anastomosis of the sinusoids of the anterior lobe there is little if any mixing of blood derived from different portal vessels and that cells in a specific part of the lobe are always fed by the same few portal vessels. This is of special interest because it has been shown that some of the cells of the anterior lobe which are known to secrete a specific type of hormone tend to be concentrated in certain areas of the lobe.[20,1] It may well be that the circumscribed areas of distribution of individual portal vessels and the distinctive grouping of cells in the anterior lobe are related features, and that together they form part of a mechanism by which the output of individual hormones from specific cells of the anterior lobe is controlled by small groups of nerve cells in the hypothalamus. For although much of the nerve tract in the pituitary stalk consists of the axons of hypothalamic nerve cells running down to the posterior lobe, there is good evidence that the axons of many such nerve cells terminate on the capillaries of the primary bed which feed the portal vessels.[7] *It is tempting, therefore, to postulate* that specific groups of neurons in a hypothalamic nucleus are linked, via the capillary loops draining into particular portal vessels, with specific groups of cells in the anterior lobe, and thus control the secretion of those particular cells.[18] That the normal functions of cells of the anterior lobe are largely maintained by neurohumoral stimuli received directly from the hypothalamus is well seen when the lobe is deprived of such stimuli, as, for example, by section of the pituitary stalk and the insertion of a plate to form a permanent barrier between its cut ends. With the passage of time after this operation the cells in the areas which escape infarction become very small,[2,4] and there is a severe loss or even a complete disappearance of the intracytoplasmic granules which are normally seen and indicate hormonal activity.[23,4] The altered appearance of the cells is presumably due to the change in their environmental conditions. For although these cells continue to receive blood from the short portal vessels, the latter are now draining a capillary bed which has been denervated (since the axons which end on this bed have been cut in the stalk) and consequently the blood which these vessels carry no longer contains the neurohumors of hypothalamic origin which it normally transports.

Although all of the details of the way in which hypothalamic control of the anterior pituitary is achieved are not yet known, one factor is undoubtedly essential, namely, the presence of intact connections, vascular and neural, between brain and gland. When these connections have been permanently interrupted, as by section of the stalk and the insertion of a plate, not only is the pituitary gland itself affected, but striking changes also occur elsewhere in the body.[23,7] For example, there is a marked retardation of bodily growth in young animals, and individual organs, such as the heart, kidneys, liver, and intestines, all fail to grow to their normal size. Metabolic disturbances are pronounced and may include severe hypoglycemia.[23] Atropic changes occur in the organs under pituitary control, the target organs most severely affected being the gonads, the accessory sex organs, and the cortex of *the adrenal glands. Many of the remote* changes caused by section of the stalk are indeed essentially equivalent to those observed after actual removal of the pituitary.[19,20]

The posterior lobe is equally dependent for its normal functioning on having an intact connection with the hypothalamus. In this case the connection is entirely a neural one, the nerve tract running down in the pituitary stalk. When the pituitary stalk is cut, this connection is severed, of course, and as a result of its denervation the posterior lobe atrophies, although its blood supply remains intact.[23,24,25] The immediate effect of this denervation is to induce a severe diabetes insipidus, a result which shows clearly that the output of antidiuretic hormone from the posterior lobe is under hypothalamic control. A

similar polyuria is not infrequently seen in cases of head injury and this is due to the nerve tract to the posterior lobe having been damaged[17 18]

On the pathologic side an understanding of the detailed vascular anatomy of the pituitary particularly as demonstrated by the effect of section of the stalk provides an explanation for the changes seen in the gland in cases of postpartum necrosis of the anterior pituitary For the infarct seen in the first few days after section of the stalk is so remarkably similar in extent and position to the lesion found in acute cases of postpartum pituitary necrosis[24] that one must assume that the necrosis occurring postpartum is due to a failure of the circulation through the long portal vessels of the stalk caused by some factor associated with the abnormal termination of the pregnancy Similarly a failure of the circulation through this same group of portal vessels possibly associated with a low blood pressure must also be the cause of the massive anterior pituitary necrosis which is occasionally found in patients suffering from diabetes mellitus That the flow of blood through the portal vessels in the stalk can vary very considerably has been shown by Worthington[26 27] who watched these vessels directly in living animals observing the effects of various distant stimuli and drugs However much still remains to be discovered about the flow of blood through the pituitary and the various influences to which the circulation of this vital organ is subject both in health and in disease but the small size of the gland and its inaccessible situation make the investigation of these problems unusually difficult

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# Clinical communications

## The electrocardiogram of young Nigerians

*O Seriki MB MPCP Ed*
*A J Smith BM MRCP**
*Lagos Nigeria*

During a survey of arterial hypertension in the Lagos University Teaching Hospital Nigeria[1] it became apparent that no criteria exist for the interpretation of the electrocardiogram of the Nigerian subject apart from those found in European or American texts

Several observers have recorded variants of the normal electrocardiogram in Africans and in those of African descent Trowell[2] describing two of these comments that in most parts of Africa clinicians have studied the E C G in a large number of Africans and have been unable to detect the abnormalities (sic) that occur in South Africa it is unlikely that these abnormalities occur or occur commonly in other countries in Africa However there have been reports of similar variants not only from South Africa [4] but also from Uganda in East Africa[5]

Peculiarities of the S T segment in precordial leads have been recorded in normal American Negroes[6,7] although Phillips and Burch[8] comment little on variations in the electrocardiographic pattern in the course of their review of racial differences in the incidence and presentation of cardiovascular disease

This paper records our findings in healthy West African children and young adults in Lagos Nigeria

### Material

The first 100 electrocardiographic tracings were recorded from 50 female student nurses (mean age of 19 3 years) and 50 male medical students (mean age of 24 0 years) All had been medically examined and found to be healthy on admission to either nursing or medical school and none had a past history of rheumatic fever or symptoms suggesting a cardiac lesion The heart was examined and the blood pressure measured after the electrocardiogram had been recorded and chest x ray films were available for all of the subjects

Electrocardiograms from 202 school children 8 to 16 years of age were recorded in two local schools The numbers of boys and girls in each age group are shown in Table I It was not possible to investigate each of these children in detail but examination of the cardiovascular system re

*Table I Age and sex distribution of 202 Nigerian school children*

| Age (yr) | Male | Female |
|---|---|---|
| 8–9 | | |
| 10–11 | 40 | 40 |
| 12–13 | 44 | 16 |
| 14–16 | 50 | — |
| | 12 | — |

From the Department of Medicine University of Lagos Medical School, Lagos Nigeria
Received for publication on Oct 25 1968
Address Department of Therapeutics, Royal Infirmary Sheffield 6 England

vealed no abnormality in any of them. A standard 12 lead electrocardiogram was taken with the subject lying comfortably on a couch. A Phillips Cardiopan 1 machine was used, although some of the electrocardiographic variants were recorded again when a Cambridge direct writing portable apparatus was used in order to exclude mechanical artefact as a source of the unusual tracings.

**Results**

All of the subjects were normal on examination with blood pressures well within the accepted range. All chest x-ray films were normal.

Most of the standard electrocardiographic measurements conformed to the accepted American or European pattern. In particular, the duration of the P-R and Q-T intervals, the length of the QRS complex, and the height of the P and T waves corresponded well with findings obtained in other countries.

*Electrocardiograms from young adults*

1. AXIS DEVIATION. Mean frontal plane axis was calculated from the standard triaxial reference system. A frequency/distribution diagram was drawn for each group of students separately and in combination and is shown in Fig. 1. This is within normal limits.

2. ELEVATION OF S-T SEGMENT. Among the 50 student nurses no electrocardiogram showed elevation of the S-T segment by more than 2 mm. from the isoelectric line in any lead. In the male students S-T segment elevation in excess of 2 mm. with a concave form ending in a tall positive T wave was common, occurring in 17 cases (34 per cent) in precordial Lead $V_4$. It appeared less frequently in Leads $V_3$ and $V_5$ and was not apparent in standard or augmented unipolar limb leads.

This elevation was persistent over a period of 6 months and was not affected by exercise in the 3 subjects in whom this was studied. A typical electrocardiogram showing this feature is reproduced in Fig. 2. This corresponds closely with the variants described by Goldman[6] in America and as Pattern II by Grusin[7] in South Africa.

The differing sex incidence of this variant might be related to age (the medical students were on an average 5 years older than the nurses) but was also reported by Grusin.[7] In his series 27 per cent of 200 male patients showed S-T segment elevation, although it was present in only 2 (4 per cent) of 50 female nurses.

In our series the frequency of S-T segment elevation bore no relationship to tribal origin or to hemoglobin genotype. (Twenty per cent of the subjects were of AS genotype, the rest were AA—roughly the same proportion as that existing in the general population in Nigeria.)

3. INVERTED OR BIPHASIC T WAVES

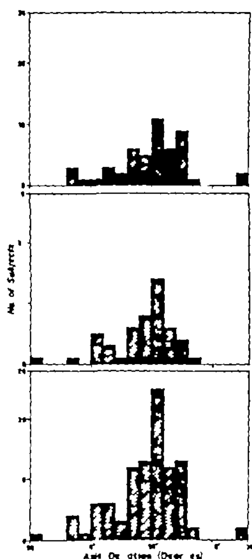



Fig. 1. Frequency/distribution diagram of axis deviation (mean frontal plane) in 50 male students (*top*), 50 female nurses (*center*), and both groups in combination (*bottom*).

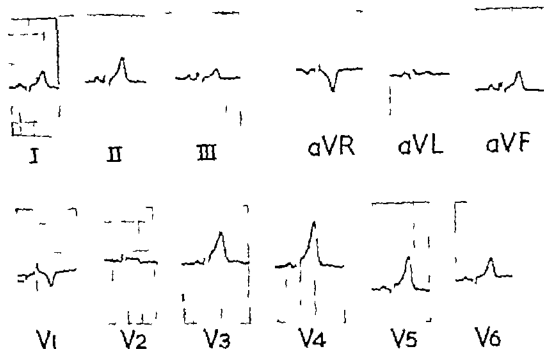



Fig. 2 Electrocardiogram of healthy male Nigerian student showing elevation of S-T segment in precordial leads

Inverted or biphasic T waves were often found in the right precordial leads (in 92 per cent of cases in Lead $V_1$ and in 51 per cent in Lead $V_2$). The T waves were frequently deeply inverted and asymmetrical with long sloping proximal limbs and relatively sharp distal ascent to the isoelectric line. Inverted T waves in Leads $V_1$ and $V_2$ are not uncommon outside Africa but it is unusual to find inversion extending to Leads $V_3$ and V. In this series 7 subjects had inverted T waves in either Lead $V_3$ or Lead V or in both.

4. LEFT VENTRICULAR HYPERTROPHY. In 3 normotensive subjects with no signs of left ventricular hypertrophy the combined magnitude of $R_{V5}$ and $S_{V1}$ was well in excess of 40 mm. In young people this may occasionally have no significance but it is included here since both Grusin[3] and Somers and Rankin[3] recorded this pattern in normal subjects from other parts of Africa.

*Electrocardiograms from school children.* No additional variants were found in these subjects and they conformed to the standard pattern in most respects.

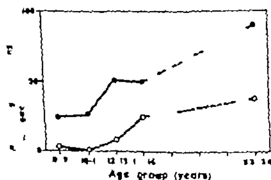



Fig. 3 Percentage incidence of electrocardiograms showing S-T segment elevation in the age groups examined. *Solid-dot curve*: Elevation in any lead of less than 2 mm. *Open-dot curve*: Elevation in any lead of more than 2 mm.

1. S-T SEGMENT ELEVATION. The percentage incidence of S-T segment elevation of 1 and 2 mm or more in any lead is plotted against age in Fig. 3. It can be seen that the incidence of elevation of the S-T segment increases with age. Although it was not possible to examine many girls over the age of 11, S-T segment elevation

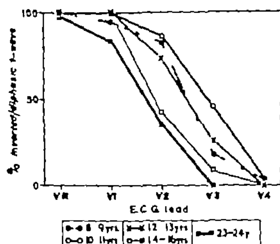



Fig. 4. Percentage incidence of inverted/diphasic T waves in right and mid precordial leads related to age in 302 normal Nigerian subjects.

was notably more frequent in boys below that age.

2. INVERTED OR DIPHASIC T WAVES. Inverted or biphasic T waves were commonly seen in precordial leads on the right side. The percentage incidence in each of five leads is related to the age of the subject in Fig. 4. It can be seen that this pattern becomes less prominent with increasing age after 11 years.

## Discussion

Our findings in Nigeria are similar to those from South and East Africa and from American Negro populations. The particular variants described have been recorded previously by clinicians working in Africa but not, in so far as we know, from the West African coast.

The significance of these patterns is obscure. Elevation of S-T segments which may cause considerable diagnostic confusion[7] is apparently acquired during late childhood and adolescence and is more prominent in males than females. It seems to be unlikely that it is related to cardiac disease since all of our subjects were healthy and gave no history of previous illness apart from recurrent pyrexia attributed to malaria and occasional gastroenteritis.

On the other hand, inversion of T waves in right precordial leads becomes less common with increasing years. It has been described as the persistence of a juvenile form in American Negroes[10,11] and our findings support this suggestion.

The importance of racial variants in the electrocardiogram and their confusion with truly abnormal tracings has been stressed by Goldman.[14] It seems to be likely that the patterns which we have found in Nigeria will be found among Africans and those of African descent whenever systematic search is made for them.

## Summary

Examination of the electrocardiograms of 100 students and 202 school children in Lagos, Nigeria, revealed a high incidence of S-T segment elevation in precordial leads increasing with age and occurring more commonly in males.

Biphasic or inverted T waves were found commonly in precordial leads on the right side, occasionally extending as far as Lead $V_4$. This is less common in older subjects and may represent a persistence into young adult life of a juvenile form.

These normal appearances deserve wider recognition in order to prevent confusion in interpretation of the electrocardiogram.

We would like to thank the student volunteers and teachers at the local schools and to acknowledge the help given by Dr. T. Oluwole, Staff Medical Officer, who made available medical records, x-ray films, and hematological investigations. Professor G. L. Monekosso gave helpful advice, and the British Heart Foundation provided financial support for this and related investigations carried out in the Department. Figures were prepared by the Department of Medical Illustration, University of Lagos Medical School.

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# Congenital aortic sinus aneurysms

## With particular reference to dissection of the interventricular septum

*Altan Onat, M.D., M.S., F.C.C.P.*
*Orhan Ersanlı, M.D.*
*Aykan Kanuni, M.D.*
*Jale B. Aykan, M.D.*
*Istanbul, Turkey*

Aneurysms of the aortic sinus of Valsalva may be congenital, syphilitic, or due to bacterial endocarditis. The latter two etiological types appear to be decreasing in frequency. Congenital aneurysms of the aortic sinuses were considered to be a rare entity, yet the sharply increasing number of cases reported in the literature during the past quarter century indicates that this lesion is more common than was formerly believed. Sakakibara and Konno[1] stated that, after the first detailed description of this entity by Thurnam in 1840, only 18 similar cases were reported in the subsequent 100 years; in the following two decades, however, 19 and 51 cases were reported, adding up to a total of 88 cases by 1960. Since then the tendency to geometric increase has not ceased; we were able to trace in the literature 82 additional new cases of congenital aortic sinus aneurysm[2-19] in the 4 years up to 1964.

A congenital aortic sinus aneurysm protrudes in a diverticular fashion and commonly penetrates into a low pressure area, usually into the right ventricle or right atrium, rarely into the pulmonary artery, pericardial sac, left atrium, or left ventricle. However, aorticocardiac fistulas involving a large aneurysm lying within the interventricular septum have rarely been recorded and have not received adequate attention. The following report concerns 2 patients in whom a fistulous communication existed between the right coronary sinus and a large aneurysm occupying primarily the muscular portion of the interventricular septum. Secondary penetration occurred into the right ventricular outflow tract and into the left ventricle, respectively.

### Report of cases

*Case 1.* A 26-year-old farmer was admitted to our Department on March 11, 1965, with the chief complaint of exertional dyspnea, palpitation, and swelling of the ankles of 1½ months' duration. He had been active in his work on the farm and free from complaints until the onset of his present illness. He stated that he had been found fit during a medical examination in 1959 for military service, which he performed fully for 2 years. His complaints started without an abrupt onset sometime late in January, 1965, when progressively increasing exertional dyspnea and palpitation were first noticed, followed by dyspnea at rest and, more recently, by an aching pain in the right hypochondrium and swelling of the lower extremities.

On physical examination the patient appeared to be dyspneic. The neck veins were distended and

From the Department of Medicine and Pathology, Cerrahpaşa Hospital, Medical School, University of Istanbul, Istanbul, Turkey.
Received for publication Oct. 23, 19[illegible].

a moderate degree of soft pitting bilateral pretibial edema was present The pulse was of collapsing type and the blood pressure measured 135/50 mm Hg There was a slightly increased left ventricular activity and a moderate precordial hea e Auscultation revealed frequent premature beats and a superficially appearing Grade 6/6 continuous murmur with systolic and diastolic accentuation The murmur had its greatest intensity in the third intercostal space to the left of the sternum and was transmitted to the second and fourth left intercostal spaces A continuous thrill was associated which was more intense in diastole The liver was enlarged 3 fingerbreadths below the right costal margin was tender and disclosed systolic pulsation The patient remained afebrile throughout the period of observation The phonocardiogram (Fig 1) confirmed that the continuous murmu exhibited a systolic and a diastolic peak of intensity with greater accentuation of the dia tolic murmur The electrocardiogram showed frequent multifocal premature ventricular beats A focal intraventricular block was present in which a wide angle ex ted between the mean initial (−60 degrees slightly anterior) and terminal (−70 degrees posterior) 0 04 second QRS ectors Signs of ventricular hypertrophy were absent X ray films of the chest and fluoroscopy revealed a moderate enlargement of both entricles and an increase in lung vascular markings The jugular venous pres ure measured 24 cm $H_2O$ Blood counts sedimentat on rate urinalysis and serum electrolytes were within normal limits Serologic tests for syphil s and blood cultures remained negative

Evidently the patient had an aortic leakage w th a left to right shunt In view of the rapid development of congestive failure in this patient who had

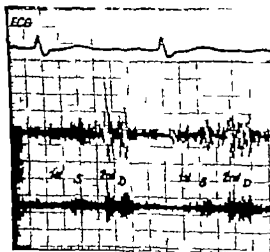



Fig 1 Case 1 Phonocardiogram recorded in the third left intercostal space demonstrates a to-and fro type of murmur with a systolic (S) and diastol c (D) peak of intensity

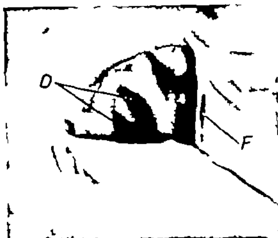



Fig 2 Case 1 Close up of the right aortic sinus of Valsalva show the openings (O) communicating with the aneurysm nd the fenestrations (F) of the cusp

shown no previous cardiac disability and the superficial continuous murmur w th two peaks of intensity a presumptive diagnosis of aortic sinus aneurysm with rupture into the right entricular outflow tract was made The patient was put on a low sodium diet and bed rest Cedilanid and low doses of chlorothiazide were given in preparation for retrograde aortography and sub equent at tempt t surgical repair Signs of congestive failure diminished but myocardial irritabil ty persisted as evidenced by relatively frequent ventricular premature beats On March 21 the night before the scheduled aortography the patient died suddenly presumably from entricular fibrillation or possibly from cardiac arrest secondary to complete heart block

NECROPSY The heart we ghed 400 grams Both ventricles were dilated the right entricle had a maximal thickness of 6 mm and the left 5 mm The right aortic cusp exhibited two small fenestrations (Fig 2) In the central third of the right coronary s nus there were two openings which mea ured 6 by 9 mm and 10 by 10 mm (Fig ) A third opening 2 mm in diameter existed f rther below All three openin communicated w th a aneurysmal ca ity 6 6 by 6 4 by 5 5 cm in size occupying in part the membranous interventri ular septum and the upper portion of the mu cular septum and partly extending into the ter or wall of the left ventricle (Fig 3) The neurysm had a glisten g lining Ne ther the aneurys m the aort alve showed ny egetations The portion of the aneurysm just below the right coronary sinus was separated from the left ventricular ca ty by fibromuscular wall 2 to 3 mm in thickness The aneurysm bulged into the outflow tract of the ght en tricle ( n an area extending from just below the pulmonary valve down to the beg nning of the papillary muscle of the septal leaflet of the tricuspid valve) On th wall of the aneurysm a 6 tula




Fig. 3. Case 1. View from the left ventricle. Congenital aneurysm (A) of the right coronary sinus (*RCS*) lying within the muscular portion of the interventricular septum (*VS*) and partly extending into the anterior wall of the left ventricle (*LV*).




Fig. 4. Case 1. View from the right ventricle. Fistulous opening at the crista supraventricularis (*CS*) in communication with the aneurysm is indicated by probe. Three further openings (*O*) are situated just below *PV*, Pulmonary valve.

4 by 2 mm. existed at the crista supraventricularis and three additional fistulas (measuring 6 by 6, 2 by 2, and 9 by 4 mm.) just below the supraventricular crest (Fig. 4). The coronary arteries as well as the lining of the aorta and pulmonary artery presented no abnormalities.

The rest of the necropsy disclosed congestion of the lungs, liver, and kidneys. A caseous tuberculoma of the pancreas and tuberculous peripancreatic lymph nodes were found.

HISTOLOGIC EXAMINATION. Histologic examination of the aneurysmal wall revealed a layer of fibrin below which existed connective tissue interspersed with lymphocytes, plasma cells, histiocytes, and newly formed capillaries. The neighboring myocardium demonstrated scattered fibrous areas and inflammatory areas consisting of mononuclear cellular infiltration. Inflammatory cellular infiltration was not seen in areas of the myocardium remote from the aneurysm.

*Case 2.* The clinical information available on this patient is limited. A 32-year-old male laborer, he was seen elsewhere as an outpatient in June, 1961, because of dyspnea and palpitation. The apex beat was palpated at the sixth left intercostal space, 1 fingerbreadth outside the midclavicular line. An intense systolic murmur was heard both at the left parasternal area and at the apex. An electrocardiogram showed right bundle branch block. The cardiac size was increased roentgenographically. Repeated follow-up examinations disclosed the development of atrioventricular dissociation in February, 1965. When he was hospitalized in April, 1965, because of an increase in dyspnea and palpitation, his pulse rate was 40 per minute and blood pressure 120/60 mm. Hg. A mild diastolic murmur was noted in

addition to the previous cardiac findings. The edge of the liver was palpable 2 fingerbreadths below the costal margin. Serologic tests for syphilis were negative. Blood leukocyte count and sedimentation rate remained normal and urinalysis was negative as they were during his previous visits. Throughout his stay in the hospital the patient remained afebrile. He complained of retrosternal discomfort and exhibited paranoid ideas. One day prior to his death he experienced two episodes of syncope associated with urinary incontinence. On May 24 the patient died.

NECROPSY. There was hypertrophy and marked dilatation of the left ventricle which had a wall thickness of 20 mm. The right ventricle showed marked hypertrophy and dilatation, its wall measured 7 mm. The right aortic cusp exhibited only a narrow rim of cusp tissue (hemorrhagic necrosis) (Fig. 5). The right coronary sinus presented as a large pouch which was distended by thrombus. This pouch extended into a large cavity which measured 7 by 7 by 6 cm and occupied the interventricular septum. The aneurysmal cavity was full of thrombi of mixed type. It extended from the aortic annulus fibrosus down to a level 8 cm away from the apex and from the anterior wall of the septum to the posterior aortic cusp. The aneurysm bulged toward the pulmonary conus obstructing its lumen considerably. Posteriorly it protruded toward the base of the right atrium narrowing it at the level of the septal leaflet of the tricuspid valve. The septal leaflet was absent, presumably fused to the surface of the aneurysmal protrusion which presented marked endocardial thickening. Remnants of a few chordae tendineae extended in this direction (Fig. 6). The endocardium of the left ventricle was markedly thickened in an area lying below the right aortic cusp and anterior to it. Here a fistulous opening communicated with an extension of the aneurysmal cavity in the anterior wall of the left ventricle. Farther below an area of hemorrhagic necrosis was noted in a region in which the wall of the aneurysmal cavity was very thin (Fig. 5).

HISTOLOGIC EXAMINATION. Histologic examination of the aneurysmal wall and the neighboring myocardium revealed extensive fibrosis with loosely diffuse and focal inflammatory reaction accompanied by hemorrhage, and very few capillaries. Small fibrous areas were present in other regions of the myocardium. The tip of the major papillary muscle of the left ventricle demonstrated larger fibrous areas. The lungs disclosed lobular pneumonia, old pleural thickening and adhesions. The liver was markedly edematous. The kidneys, adrenal gland and spleen as well as other organs and mucous membranes showed severe hyperemia and ed ma




Fig. 6. Case 2. Right ventricular view. The anterior (TA) and the posterior (TP) tricuspid leaflets are visible and at the site of the septal leaflet the protrusion of the aneurysmal wall (A) is apparent. The septal leaflet is missing, presumably secondary to pressure of the aneurysmal protrusion and fusion with the surface of the aneurysm. Chordae tendineae (Ch) extending to the absent septal leaflet are barely visible.




Fig. 5. Case 2. Congenital aneurysm of the right coronary sinus with intramural rupture and secondary penetration (R) into the left ventricle (LV). Only a narrow rim of the right aortic cusp (C) exists. Below this cusp is a large area of endocardial fibrosis covering the large aneurysm in the muscular portion of the interventricular septum (S) and in the middle of which is a small area of hemorrhagic necrosis (N).

**Discussion**

In the majority of cases of congenital aortic sinus aneurysm the lesion assumes the form of a diverticular protrusion into a cardiac cavity. The two cases presented in this paper were unusual in that in each instance a large aneurysm was contained within the muscular portion of the ventricular septum. It has been pointed out[1,8,14] that congenital aneurysms are small and are almost always confined to the right coronary sinus and adjacent two thirds of the noncoronary sinus and that they commonly rupture to form aorticocardiac fistulas. On the other hand acquired aneurysms may arise from any of the aortic sinuses, are large in size, tend to extend upward and often rupture outside the heart. Although the involvement of the ventricular septum by a large aneurysm may lead one to suspect the presence of an acquired cause, there was no clinical or autopsy evidence of an acquired cause in our cases. Consequently both aneurysms may be justly considered to be congenital in origin. Gibbs and Harris[4] described the case of a patient who had a congenital aneurysm of the left and right coronary sinuses. The aneurysm dissected the ventricular septum forming a large cavity, the lower portion of which was described to be in the muscular portion of the septum. *There was no perforation into a cavity* and the patient died from aortic regurgitation and cardiac failure due to congenital absence of the right aortic valve cusp. Individual cases of congenital aortic sinus aneurysm with intramural rupture and dissection of the membranous portion of the interventricular septum have also been described by Lian[17], Warthen[18], Lee[19], Orbison and Mostofi[20] and Kay.[3] Secondary penetration into the left atrium occurred in one of these cases[17] and into the left ventricle in two.[17,18] Sakakibara and Konno[5] suspected that this type of aneurysm developed after intramural rupture of a congenital aneurysm with subsequent formation of a hematoma and organization. They considered this variety of case to be representative of a pseudoaneurysm. The pre-existence of an additional localized area of fragile tissue at this portion of the interventricular septum is postulated to explain the intramural rupture of the aneurysm instead of protrusion into a cardiac cavity.

Clinically, aneurysms which dissect the ventricular septum present few distinctive features as compared to those which do not. Worthy of emphasis is the more frequent occurrence of atrioventricular conduction disturbances. Although *A V block*, A V nodal rhythm and right bundle branch block have been reported occasionally in cases of congenital aortic sinus aneurysm[1,12,13] particularly in those instances in which the aneurysm protrudes or penetrates just above or below the tricuspid valve, conduction defects appear to be very common in cases of aneurysm involving the ventricular septum. Focal intraventricular block occurred in Case 1 and complete atrioventricular dissociation in Case 2. These changes were presumably due to the encroachment of the aneurysm on the septum where the specialized conduction system is most densely concentrated. In the case of Lee and associates[19] death resulted from complete heart block which was believed to be due to hemorrhage into and inflammation of the conduction system. Bundle branch block was observed in the cases reported by Warthen[18] and Gibbs and Harris.[4]

In the two cases presented herein the aneurysms dissecting the ventricular septum *penetrated into the outflow tract of* the right ventricle and into the left ventricle respectively. *In this connection* we have attempted to review the cases of congenital aortic sinus aneurysms reported in the world literature since the last comprehensive survey[5] of this field appeared in the English literature. The sites of origin and penetration of the aneurysms are listed in Table I. The left ventricle is a rare site of termination, namely in one* out of 67 instances of ruptured aneurysms.* Although congenital aneurysms of the aortic sinuses penetrate far more frequently into the right cardiac cavities, such a predilection is not observed in the limited number of cases with dissection of the ventricular septum. Reasons of topographic proximity should account for this difference.

*For cases [illegible] prior [illegible] 1960 [illegible] of Sakakibara and Konno.[5]

*Table 1 Sites of origin and penetration of congenital aortic sinus aneurysms in 77 cases**

| *Site of origin* | *Number of cases* | | *Site of termination* | *Number of cases* |
|---|---|---|---|---|
| | *Unruptured* | *Ruptured* | | |
| Right coronary sinus | 4 | 47 | Right ventricular outflow tract | 24 |
| | | | Right ventricular inflow tract | 10 |
| | | | Right atrium | 11 |
| | | | Pulmonary artery | 2 |
| Noncoronary sinus | 1 | 15 | Right atrium | 11 |
| | | | Right ventricle | 3 |
| | | | Left ventricle | 1 |
| Left coronary sinus | 1 | 4 | Right atrium | 3 |
| | | | Left atrium | 1 |
| Unknown | | 1 | Right atrium | 1 |
| Right and noncoronary sinuses | 2 | | | |
| Right and left coronary sinuses | 1 | | | |
| All three coronary sinuses | 1 | | | |
| Total | 10 | 67 | | 67 |

*Cases [illegible] reported since 1960 have been included [illegible]. The [illegible] reported [illegible] by the French authors have been counted [illegible] cases. [illegible] fistula with [illegible] aneurysmal sac are not included.

Unless other congenital cardiac anomalies are associated an aneurysm of the sinus of Valsalva remains silent until it ruptures or leads to bacterial endocarditis. Coronary insufficiency with myocardial infarction[10] conduction disturbances functional pulmonary stenosis[8,11] tricuspid insufficiency obstruction to tricuspid inlet and pulmonary emboli originating in the right atrium[13] have been recorded as rare complications of unruptured aortic sinus aneurysms. The development of aortic regurgitation is a more frequent observation.[4,14] The basis for regurgitation in our second case was loss of substance exclusively of the right anterior aortic cusp. This was thought to be due to the mechanical effects of the turbulent blood stream on this cusp which had been distended by thrombus in that sinus and which protruded toward the orifice. Tricuspid insufficiency has been noted occasionally in cases of ruptured aneurysm of the aortic sinus even in the absence of right ventricular failure. However the observation in Case 2 namely absence of the septal leaflet of the tricuspid valve presumably secondary to fusion with the surface of the aneurysmal protrusion has not been previously recorded to our knowledge.

In view of the known risks to which patients with ruptured aortic sinus aneurysm are exposed and their poor prognosis in general surgery is recommended in each case and is a matter of urgency in the more severe cases in patients with heart failure.[8] Surgical treatment has progressed to complete occlusion of the fistula and reconstruction of the aortic root using extracorporeal circulation alone or combined with hypothermia. The results have been fairly satisfactory. However surgical correction of an aneurysm lying within the muscular portion of the interventricular septum entails evident and major problems. In this instance the usual procedure of closure by suturing and placing a patch for reinforcement of the ruptured area would be unsatisfactory for a long period of time since the underlying aneurysmal cavity would persist and offer no support. A more radical operation namely total replacement of the aortic valve might be needed and prove to be more satisfactory.

This would involve closure of the fistula from the aortic side its reinforcement by the cuff of the prosthesis and correction of the frequently associated aortic regurgitation in addition to simple closure of the fistula from the right or left ventricular side A reopening of the fistula might thereby be prevented even though the aneurysmal cavity is left alone

## Summary

Two cases of ruptured congenital aneurysm of the sinus of Valsalva have been reported in which a large aneurysm dissected the muscular portion of the interventricular septum Penetration through the crista supraventricularis occurred in one case and into the left ventricle in the other case In the latter patient the septal leaflet of the tricuspid valve was absent because of fusion with the protruded aneurysmal surface and aortic regurgitation was associated Conduction disturbances were present in both cases The relationship of congenital aortic sinus aneurysms in general to those involving the ventricular septum was discussed Problems pertaining to surgical correction of aneurysms of the latter type were pointed out

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# Hematocrit, plasma protein, plasma volume, and viscosity in early hypertensive disease

*Gösta Tibblin, M.D.**
*S. E. Bergentz, M.D.*
*J. Bjure, M.D.*
*L. Wilhelmsen, M.D.*
*Göteborg, Sweden*

There are two major factors which determine the level of the arterial blood pressure, namely, the volume of blood flow through the arteries per unit of time and the resistance to the blood flow offered by the arterioles and the capillaries. The circulating blood volume and the blood viscosity have been considered to be of secondary importance.

In 1905 Gaisböck[7] applied the term "polycythemia hypertonica" to a group of hypertensive patients with elevated red blood cell count. Reports of so-called benign polycythemia have been published by Lawrence and Berlin[16] and Russell and Conley.[17]

A positive and significant correlation between hematocrit and diastolic blood pressure has been reported by McDonough and associates.[14] In the Men of 1913—a population study of 973 men all born in 1913[8]—an increased hematocrit and an elevated total plasma protein were found in subjects with diastolic blood pressure $\geq$ 100 mm. Hg.

The purpose of the present study was to investigate in more detail this apparent tendency to hemoconcentration in early hypertensive disease in a series of hypertensive individuals taken from the subjects investigated in that study,[18] and to use as controls normotensive individuals from the same population.

## Material

The Men of 1913 Study is a population study of 973 men all born during 1913 and living in Göteborg, Sweden. The prime interest was centered upon the early manifestations of chronic disease. During 1963, 88 per cent of the subjects selected at random were examined at this hospital. The examination was a 4-hour study of the individual's state of health, using the personnel and technical resources of the hospital. Among the variables investigated as being of special interest to the present study were the following: hematocrit (Wifug, Stockholm), total plasma protein (Biuret), blood pressure, eyeground (examination by an ophthalmologist), heart volume, electrocardiogram, kidney function, and skinfold thickness.

During the autumn of 1964, the subjects with elevated systolic and diastolic blood pressure were re-examined. The hyperten-

From the First Medical Service, First Surgical Service, and the Department of Clinical Physiology, Sahlgrenska Sjukhuset, University of Göteborg, Göteborg, Sweden.
This study was supported by grants from the Insurance Company Förenade Liv.
Received for publication Oct. 29, 1968.
*Address reprint requests to: Dr. Gösta Tibblin, First Medical Service, Sahlgrenska Sjukhuset, Göteborg, Sweden.

*Table I Blood pressure hematocrit total serum proteins and subscapular skinfold in the normotensive and hypertensive subjects when examined in 1963 (Goteborg study 1963)*

| Subjects | Systolic blood pressure | Diastolic blood pressure | Hematocrit | Serum protein | Subscapular skinfold |
|---|---|---|---|---|---|
| Normotensive | | | | | |
| x | 124 | 80 | 43 3 | 7 01 | 13 |
| s | 11 | 8 | 4 7 | 0 20 | 5 |
| n | 11 | 11 | 11 | 11 | 11 |
| Hypertensive | | | | | |
| x | 181 | 112 | 43 8 | 7 29 | 23 |
| | 14 | 10 | 2 2 | 0 34 | 11 |
| n | 14 | 14 | 14 | 14 | 14 |
| p | <0 001 | <0 001 | <0 05 | <0 05 | <0 01 |

[illegible]

sive group of the present study was selected from these subjects The criteria used in choosing the hypertensive subjects were untreated individuals with blood pressure of $\geq 150$ $\geq 110$ mm Hg and hypertensive changes in eyeground (attenuated arterioles and or changes in caliber) Sixteen subjects fulfilled these criteria and 14 took part in the study From the normotensive population without heart disease examined in 1963 14 men were selected at random and asked to take part in the study as controls and of these 12 men accepted Since complete study of one of these could not be made this subject was subsequently excluded from the control material

Blood pressure hematocrit total serum proteins and subscapular skinfold values for these 14 hypertensive and 11 normotensive subjects at the time of the 1963 examination are given in Table I

The total serum proteins and subscapular skinfold were significantly increased in the hypertensive group In the hypertensive group the mean value for the hematocrit was 45 8 per cent as compared with 43 3 for the normotensive group ($p < 0$ 05)

It can be seen therefore that it was possible to investigate two groups from the same population of the same age and sex The hypertensive group can be considered to be representative of the untreated hypertensive individuals and the control group to be representative of the normotensive subjects in the same population The subjects in both groups were without complicating diseases such as anemia heart failure kidney diseases or pulmonary diseases Heart volume kidney function and respiratory function were normal in all subjects All subjects except one hypertensive individual were working full time when studied in 1964 The subjects in the hypertensive group were in the early stage of manifest hypertensive disease with hypertensive changes in eyeground but without severe manifestations from other organs

**Procedure**

All subjects were studied during the months of October and November 1964 and always at the same time of the day About 4 hours had elapsed since their last meal After arrival at the laboratory they were allowed to rest in the recumbent position for about 15 minutes The investigation was performed with the subject in the supine position on a table with his feet on the pedals of a bicycle ergometer The pedals were placed 15 cm above the level of the table

A polyethylene catheter was introduced into an antecubital vein by means of a modified Seldinger technique[18] and all samples of blood were taken through this catheter without stasis During the first 20 minutes after the injection of I[131] albumin resting values were obtained At

21 minutes the subjects started to work with a load of 600 kilogram meters per minute (kg M./min.) for 14 minutes in all subjects except one for whom a lower work load (400 k.p.m./min.) had to be chosen.

**Methods**

Blood pressures were measured with a sphygmomanometer cuff on the right arm. Diastolic blood pressure was taken as that value at which the heart sounds had completely disappeared. Mean blood pressure was estimated as diastolic pressure plus one third of pulse pressure. Heart rate was obtained from the ECG. Venous hematocrit was determined in a capillary hematocrit centrifuge at 12 000 r.p.m. for 10 minutes (Kemila, Stockholm). The mean value of two samples was used. The total plasma protein content was determined by the Biuret method. The plasma protein fractions were analyzed by paper electrophoresis in a TRIS-buffer, pH 8.9 (Aronsson and Gronwall). Plasma volume was measured with I[131] human serum albumin. Usually about 10 μC was injected (time 0) through the catheter in the brachial vein. After thorough washing of the catheter with heparin saline, samples of blood were taken from the same catheter at 5, 10, 15 and 20 minutes after injection. The plasma radioactivity of these samples as plotted semilogarithmically against time and a straight line was fitted to these points. The radioactivity at zero time was used to estimate the plasma volume. During exercise samples for the determination of radioactivity were taken at 26, 30 and 34 minutes after injection. The plasma volume during exercise at these intervals was calculated by multiplying the plasma volume at rest by the ratio of expected plasma activity over observed plasma activity at each interval.[11] The viscosity of whole blood and plasma was determined in a Brookfield synchro-lectric viscometer model LVT, equipped with a special adapter for small samples of blood. The samples of blood were withdrawn in dry heparinized tubes. Determinations were made in a water bath at 37 C, and the viscosity was calibrated against distilled water under identical conditions. The determinations were always made at four different rotational speeds, 6, 12, 30 and 60 r.p.m., representing the following shear rates: 23, 46, 115 and 230 inverse seconds.

**Results**

*From the 1963 study.* Tables II and III present the hematocrit and total serum protein values for the whole material (851 subjects) from the 1963 examination. To avoid the influence of obesity on hematocrit and total serum proteins the series is divided into quartiles according

*Table II. Hematocrit in different quartiles of subscapular skinfold for subjects with diastolic blood pressure < 100 mm. Hg and subjects with blood pressure ≥ 100 mm. Hg in the population study 1963 (n = 851)*

| | *1st quartile area 5–10 mm.* | *2nd quartile area 11–14 mm.* | *3rd quartile area 15–18 mm.* | *4th quartile area 19–40 mm.* |
|---|---|---|---|---|
| Diastolic blood pressure < 100 mm. Hg | | | | |
| $\bar{x}$ | 44.3 | 44.7 | 45.3 | 44.5 |
| s | 3.2 | 3.3 | 3.4 | 3.1 |
| n | 185 | 189 | 147 | 108 |
| Diastolic blood pressure > 100 mm. Hg | | | | |
| $\bar{x}$ | 45.7 | 46.0 | 45.2 | 45.5 |
| s | 3.5 | 2.5 | 3.1 | 3.0 |
| n | 38 | 54 | 53 | 77 |
| P | <0.05 | <0.005 | >0.05 | <0.05 |

*Table III. Total serum proteins in different quartiles of subscapular skinfold for subjects with diastolic blood pressure ≤ 100 mm. Hg and subjects with blood pressure ≥ 100 mm. Hg in the population study 1963 (n = 849)*

| | *1st quartile area 5-10 mm.* | *2nd quartile area 11-14 mm.* | *3rd quartile area 15-18 mm.* | *4th quartile area 19-40 mm.* |
|---|---|---|---|---|
| Diastolic blood pressure < 100 mm. Hg | | | | |
| x | 7.06 | 7.09 | 7.15 | 7.08 |
| s | 0.42 | 0.46 | 0.41 | 0.44 |
| n | 184 | 189 | 146 | 109 |
| Diastolic blood pressure ≥ 100 mm. Hg | | | | |
| x | 7.26 | 7.17 | 7.24 | 7.25 |
| s | 0.48 | 0.49 | 0.44 | 0.44 |
| n | 28 | 54 | 53 | 77 |
| p | <0.01 | >0.05 | >0.05 | <0.01 |

to subscapular skinfold values. The subjects with elevated diastolic blood pressure had significantly higher hematocrits in all groups except one. The mean values for the total serum proteins were higher in all groups for the subjects with elevated diastolic pressure, and the differences were significant in two groups. There was no tendency to higher differences in hematocrit and total serum proteins in the more obese subjects.

*From the present study, 1964*

ANTHROPOMETRIC DATA. Anthropometric data are given in Table IV. There was no significant difference in height, weight, and body surface area between the two groups.

BLOOD PRESSURE. Blood pressure reactions are given in Table V and illustrated in Fig. 1. The curves for the two groups are almost identical but at different levels. The systolic blood pressure of the normal subjects during exercise reaches a value which approximates the value for the hypertensive group at rest.

HEART RATES. Heart rates both at rest and during exercise were higher in the hypertensive than in the normal subjects, but the difference was not significant (Table VI). The rise during exercise was roughly the same in the two groups (Fig. 1).

VENOUS HEMATOCRIT. The venous hematocrit was significantly higher (p < 0.05) in hypertensive than in normal subjects both at rest and during exercise. After exercise the hematocrits returned to resting values in the normotensive subjects. The hypertensive group still had high hematocrit values 6 minutes after the end of the work (Table VII and Fig. 2).

TOTAL PROTEIN VALUES. The total protein values were slightly higher for the hypertensive than for the normotensive subjects at rest and during work (Table VIII and Fig. 2), but the difference was not significant. The hypertensive subjects, but not

*Table IV. Anthropometric data*

| *Subjects* | *Height (cm.)* | *Weight (kg.)* | *B.S.A. (M.²)* |
|---|---|---|---|
| Normotensive | | | |
| x | 175.9 | 73.9 | 1.88 |
| s | 6.6 | 11.1 | 0.159 |
| n | 11 | 11 | 11 |
| Hypertensive | | | |
| x | 176.5 | 84.1 | 1.99 |
| s | 5.1 | 15.2 | 0.10 |
| n | 14 | 14 | 14 |
| p | >0.05 | >0.05 | >0.05 |

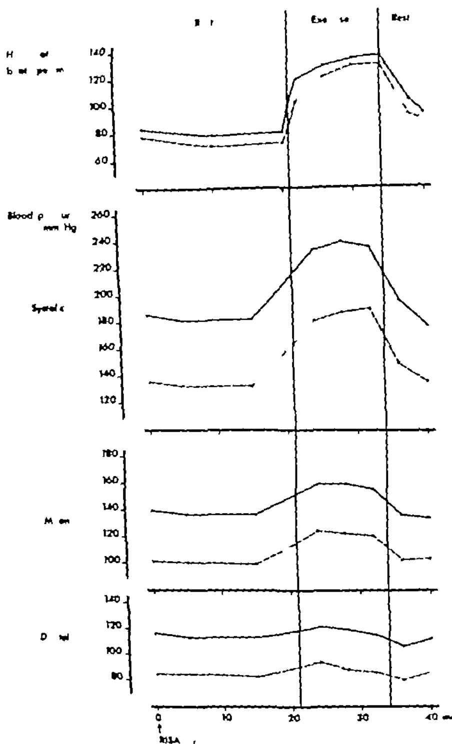



Fig. 1. Mean values for heart rate and blood pressure in normotensive subjects (*dashed line*) and hypertensive subjects (*solid line*). The mean pressure is calculated as the diastolic pressure plus one third of the pulse pressure.

*Table V. Blood pressure*

| Subjects | Rest | | | Exercise | | | Rest | |
|---|---|---|---|---|---|---|---|---|
| | 0 min | 5 min | 15 min | 24 min | [illegible] min | 32 min | 36 min | 40 min |
| Normotensive | | | | | | | | |
| Systolic blood pressure | | | | | | | | |
| $\bar{x}$ | 136 | 133 | 135 | 182 | 188 | 190 | 150 | 136 |
| s | 9 | 10 | 11 | 25 | 20 | 2? | 13 | 11 |
| n | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 |
| Mean blood pressure | | | | | | | | |
| $\bar{x}$ | 102 | 101 | 100 | 125 | 123 | 121 | 101 | 101 |
| s | 7 | 8 | 7 | 7 | 7 | 8 | 7 | 8 |
| n | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 |
| Diastolic blood pressure | | | | | | | | |
| $\bar{x}$ | 85 | 85 | 84 | 95 | 89 | 87 | 81 | 87 |
| s | 7 | 6 | 6 | 7 | 7 | 8 | 9 | 9 |
| n | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 |
| Hypertensive | | | | | | | | |
| Systolic blood pressure | | | | | | | | |
| $\bar{x}$ | 187 | 182 | 183 | 234 | 240 | 236 | 197 | 178 |
| | 15 | 18 | 14 | 27 | 24 | ?4 | 20 | 13 |
| n | 13 | 14 | 14 | 14 | 14 | 14 | 14 | 14 |
| Mean blood pressure | | | | | | | | |
| $\bar{x}$ | 140 | 137 | 137 | 160 | 160 | 156 | 137 | 135 |
| | 9 | 8 | 7 | 9 | 10 | 10 | 7 | 9 |
| n | 13 | 14 | 14 | 14 | 14 | 14 | 14 | 14 |
| Diastolic blood pressure | | | | | | | | |
| $\bar{x}$ | 117 | 114 | 114 | 123 | 120 | 116 | 107 | 113 |
| | 9 | 6 | 6 | 8 | 8 | 10 | 9 | 9 |
| | 13 | 14 | 14 | 14 | 14 | 14 | 14 | 14 |

*Table VI. Heart rate*

| Subjects | Rest | | | Exercise | | | | Rest | |
|---|---|---|---|---|---|---|---|---|---|
| | 0 min | 10 min | 20 min | 2? min | 26 min | 30 min | 34 min | 3? min | 40 min |
| Normotensive | | | | | | | | | |
| $\bar{x}$ | 76.4 | 0.6 | 72.0 | 111.9 | 1?6.6 | 129.2 | 130.1 | 93.1 | 88.9 |
| s | 12.5 | 11.6 | 11.5 | 10.9 | 17.5 | 17.0 | 18.0 | 16.5 | 18.2 |
| n | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 8 |
| Hypertensive | | | | | | | | | |
| $\bar{x}$ | 81.4 | 79.4 | 81.3 | 118.9 | 129.1 | 134.8 | 136.3 | 98.0 | 94.3 |
| s | 14.3 | 13.3 | 13.5 | 12.9 | 17.9 | 13.3 | 13.6 | 14.0 | 16.6 |
| n | 14 | 14 | 14 | 14 | 14 | 14 | 14 | 14 | 7 |
| P | >0.05 | >0.05 | >0.05 | >0.05 | >0.05 | >0.05 | >0.05 | >0.05 | >0.05 |

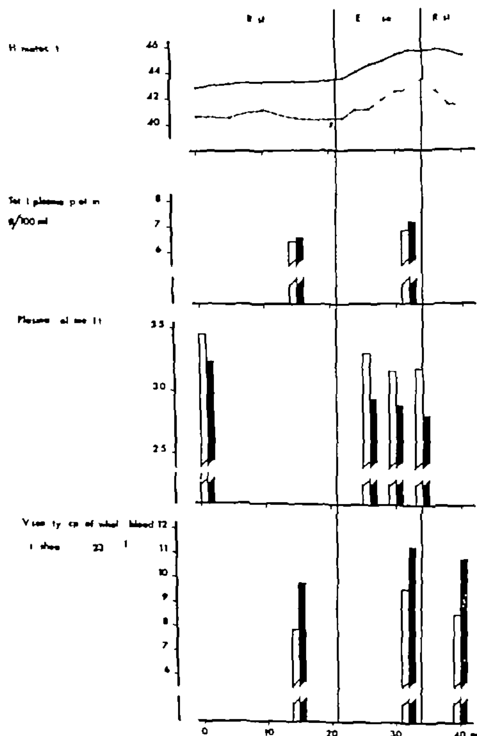



Fig. 2 Hematocrit, total plasma proteins, plasma volume and whole blood viscosity for both groups. Normotensive subjects indicated by dashed line or white bar. Hypertensive subjects indicated by solid line or black bar.

*Table VII. Hematocrit*

| Subjects | Rest | | Exercise | | | | Rest |
|---|---|---|---|---|---|---|---|
| | 0 min | 15 min | 24 min | 30 min | 3 min | 34 min | 40 min |
| Normotensive | | | | | | | |
| $\bar{x}$ | 40.7 | 40.5 | 41.2 | 42.5 | 42.7 | 43.6 | 41.5 |
| s | 2.0 | 2.3 | 2.5 | 1.9 | 2.3 | 1.5 | 2.1 |
| n | 11 | 11 | 11 | 11 | 11 | 10 | 11 |
| Hypertensive | | | | | | | |
| $\bar{x}$ | 42.9 | 43.3 | 44.6 | 45.4 | 45.7 | 45.7 | 45.3 |
| s | 1.9 | 1.9 | 1.8 | 2.2 | 2.4 | 2.7 | 2.7 |
| n | 14 | 14 | 14 | 14 | 14 | 14 | 14 |
| p | <0.05 | <0.01 | <0.001 | <0.01 | <0.01 | <0.05 | <0.001 |

*Table VIII. Total serum proteins (Gm./100 ml.)*

| Subjects | Rest (15 min.) | Exercise (34 min.) |
|---|---|---|
| Normotensive | | |
| $\bar{x}$ | 6.44 | 6.86 |
| s | 0.58 | 0.44 |
| n | 11 | 11 |
| Hypertensive | | |
| $\bar{x}$ | 6.67 | 7.21 |
| s | 0.54 | 0.54 |
| n | 11 | 13 |
| p | >0.05 | >0.05 |

the normal subjects had a significant increase in their values from rest to exercise. There was no single fraction of plasma protein which was more responsible for the elevation than any other.

ABSOLUTE PLASMA VOLUME. Absolute plasma volume was slightly lower for the hypertensive subjects at rest than for the normotensive subjects, but the difference was not significant. During exercise the absolute plasma volume decreased both for normotensive and hypertensive subjects, but the decrease was statistically significant only for the latter group. At the end of exercise the absolute plasma volume was significantly lower in the hypertensive group than in the other group (Table IX and Fig. 2). When the plasma volume was expressed per kilogram of body weight, the trend was clearer (Table X). From this it can be seen that there was a significantly decreased plasma volume at rest in the hypertensive group as compared to the normotensive. During exercise the plasma volume decreased significantly in both the hypertensive and the normotensive groups. The hypertensive group had a significantly decreased plasma volume per kilogram of body weight as compared to the normotensive group during exercise.

BLOOD VISCOSITY. Tables XI and XII give data for the viscosity of whole blood and plasma for normotensive and hypertensive subjects at the shear rate of 23 inverse seconds. Fig. 3 gives mean values for whole blood viscosity at various shear rates (23, 46, 115, and 230 inverse seconds). The viscosity both of whole blood and plasma is higher at all rates of shear in hypertensive subjects than in normotensive subjects. The difference is statistically significant for whole blood but not for plasma. Whole blood viscosity increased at all rates of shear during work in both normal and hypertensive subjects ($p < 0.05$) and returned toward resting values after work ceased (Fig. 2). The viscosity

*Table IX. Plasma volume (liters)*

| Subjects | Rest | Exercise | | |
|---|---|---|---|---|
| | | *26 min* | *30 min* | *34 min* |
| Normotensive | | | | |
| x̄ | 3 46 | 3 31 | 3 17 | 3 19 |
| s | 0 51 | 0 57 | 0 47 | 0 49 |
| n | 11 | 11 | 11 | 11 |
| Hypertensive | | | | |
| x̄ | 3 24 | 2 90 | 2 85 | 2 71 |
| | 0 35 | 0 37 | 0 35 | 0 38 |
| n | 14 | 14 | 14 | 14 |
| p | >0 05 | >0 05 | >0 05 | <0 05 |

*Table X. Plasma volume (in ml/Kg of body weight) in the normotensive and hypertensive groups*

| Subjects | Rest | Exercise | | |
|---|---|---|---|---|
| | | *26 m* | *30 m* | *34 min* |
| Normotensive | | | | |
| x̄ | 47 3 | 45 0 | 43 4 | 43 4 |
| s | 4 0 | 3 0 | 3 2 | 3 2 |
| n | 11 | 11 | 11 | 11 |
| Hypertensive | | | | |
| x̄ | 39 6 | 35 3 | 34 8 | 33 5 |
| s | 7 6 | 7 5 | 7 7 | 8 6 |
| n | 14 | 14 | 14 | 14 |
| p | <0 005 | <0 005 | <0 005 | <0 005 |

*Table XI. Viscosity (centipoise) of whole blood at shear rate of 23 inverse seconds*

| Subjects | Rest (15 min) | Exercise (32 min) | Rest (40 min) |
|---|---|---|---|
| Normotensive | | | |
| x̄ | 7 86 | 9 37 | 8 43 |
| s | 1 02 | 1 99 | 0 95 |
| n | 11 | 11 | 11 |
| Hypertensive | | | |
| x̄ | 9 86 | 11 31 | 10 90 |
| s | 0 98 | 1 50 | 1 22 |
| n | 14 | 14 | 13 |
| p | <0 001 | <0 05 | <0 001 |

*Table XII. Viscosity (centipoise) of plasma at shear rate of 23 inverse seconds*

| Subjects | Rest (15 min) | Exercise (32 min) | Rest (40 min) |
|---|---|---|---|
| Normotensive | | | |
| x̄ | 1 95 | 2 00 | 2 09 |
| s | 0 25 | 0 17 | 0 22 |
| n | 11 | 11 | 11 |
| Hypertensive | | | |
| x̄ | 2 08 | 2 14 | 1 93 |
| s | 0 37 | 0 26 | 0 25 |
| n | 14 | 14 | 13 |
| p | >0 05 | >0 05 | >0 05 |

of plasma (Table XII) increased insignificantly during work in normotensive subjects and returned toward resting values after work ceased For hypertensive subjects however the plasma viscosity decreased to below resting values after work ceased but this difference was not significant

The hypertensive group included more obese subjects than the normotensive group but the difference in weight was not significantly different between the two groups

*In order to see whether these obese* subjects could influence the results the one from the normotensive group and the five from the hypertensive group were excluded and the results were recalculated There were still significant differences in hematocrit viscosity and plasma volume per kilogram of body weight at rest The *reactions of plasma volume hematocrit* viscosity and total protein during exercise were unchanged in both the normotensive and hypertensive groups

*Table VII Hematocrit*

| Subjects | Rest | | Exercise | | | | R |
|---|---|---|---|---|---|---|---|
| | 0 min | 15 min | 16 min | 30 min | 32 min | 34 min | 40 min |
| Normotensives | | | | | | | |
| x | 40.7 | 40.5 | 41.2 | 42.5 | 42.7 | 43.6 | 41.5 |
| s | 2.0 | 2.3 | 2.5 | 1.9 | 2.3 | 1.5 | 2.1 |
| n | 11 | 11 | 11 | 11 | 11 | 10 | 11 |
| Hypertensives | | | | | | | |
| x | 42.9 | 43.3 | 44.6 | 45.4 | 45.7 | 45.7 | 45.3 |
| s | 1.9 | 1.9 | 1.8 | 2.2 | 2.4 | 2.7 | 2.[illegible] |
| n | 14 | 14 | 14 | 14 | 14 | 14 | 14 |
| p | <0.05 | <0.01 | <0.001 | <0.01 | <0.01 | <0.05 | <0.001 |

*Table VIII Total serum proteins (Gm./100 ml.)*

| Subject | Rest (15 min.) | Exercise (32 min.) |
|---|---|---|
| Normotensive | | |
| x | 6.44 | 6.86 |
| s | 0.58 | 0.44 |
| n | 11 | 11 |
| Hypertensive | | |
| x | 6.62 | 7.21 |
| s | 0.54 | 0.54 |
| n | 13 | 13 |
| p | >0.05 | >0.05 |

the normal subjects had a significant increase in their values from rest to exercise. *There was no single fraction of plasma protein which was more responsible for the elevation than any other.*

ABSOLUTE PLASMA VOLUME. Absolute plasma volume was slightly lower for the hypertensive subjects at rest than for the normotensive subjects but the difference was not significant. *During exercise the* absolute plasma volume decreased both for normotensive and hypertensive subjects but the decrease was statistically significant only for the latter group. At the end of exercise the absolute plasma volume was significantly lower in the hypertensive group than in the other group (Table IX and Fig. 2). When the plasma volume was expressed per kilogram of body weight the trend was clearer (Table X). From this it can be seen that there was a significantly decreased plasma volume at rest in the hypertensive group as compared to the normotensive. During exercise the plasma volume decreased significantly in both the hypertensive and the normotensive groups. The hypertensive group had a significantly decreased plasma volume per kilogram of body weight as compared to the normotensive group during exercise.

BLOOD VISCOSITY. Tables XI and XII give data for the viscosity of whole blood and plasma for normotensive and hypertensive subjects at the shear rate of 23 inverse seconds. Fig. 3 gives mean values for whole blood viscosity at various shear rates (23, 46, 115 and 230 inverse seconds). The viscosity both of whole blood and plasma is higher at all rates of shear in hypertensive subjects than in normotensive subjects. The difference is statistically significant for whole blood but not for plasma. *Whole blood viscosity increased at* all rates of shear during work in both normal and hypertensive subjects ($p < 0.05$) and returned toward resting values after work ceased (Fig. 2). The viscosity

*Table IX. Plasma volume (liters)*

| Subjects | Rest | Exercise | | |
|---|---|---|---|---|
| | | 26 min | 30 min | 34 min |
| Normotensive | | | | |
| x̄ | 3.46 | 3.31 | 3.17 | 3.19 |
| s | 0.51 | 0.57 | 0.47 | 0.49 |
| n | 11 | 11 | 11 | 11 |
| Hypertensive | | | | |
| x̄ | 3.24 | 2.90 | 2.85 | 2.71 |
| s | 0.35 | 0.37 | 0.35 | 0.38 |
| n | 14 | 14 | 14 | 14 |
| p | >0.05 | >0.05 | >0.05 | <0.05 |

*Table X. Plasma volume (in ml./Kg. of body weight) in the normotensive and hypertensive groups*

| Subjects | Rest | Exercise | | |
|---|---|---|---|---|
| | | 26 min | 30 min | 34 min |
| Normotensive | | | | |
| x̄ | 47.3 | 45.0 | 43.4 | 43.4 |
| s | 4.0 | 3.0 | 3.7 | 3.2 |
| n | 11 | 11 | 11 | 11 |
| Hypertensive | | | | |
| x̄ | 39.6 | 35.3 | 34.8 | 33.5 |
| s | 7.6 | 7.5 | 7.7 | 8.6 |
| n | 14 | 14 | 14 | 14 |
| p | <0.005 | <0.005 | <0.005 | <0.005 |

*Table XI. Viscosity (centipoise) of whole blood at shear rate of 23 inverse seconds*

| Subjects | Rest (15 min.) | Exercise (3[illegible] min.) | Rest (40 min.) |
|---|---|---|---|
| Normotensive | | | |
| x̄ | 7.86 | 9.57 | 8.43 |
| s | 1.0[illegible] | 1.99 | 0.95 |
| n | 11 | 11 | 11 |
| Hypertensive | | | |
| x̄ | 9.86 | 11.31 | 10.90 |
| s | 0.98 | 1.50 | 1.22 |
| n | 14 | 14 | 13 |
| p | <0.001 | <0.05 | <0.001 |

*Table XII. Viscosity (centipoise) of plasma at shear rate of 23 inverse seconds*

| Subjects | Rest (15 min.) | Exercise (3 min.) | Rest (40 min.) |
|---|---|---|---|
| Normotensive | | | |
| x̄ | 1.95 | 2.00 | 2.09 |
| s | 0.23 | 0.17 | 0.22 |
| n | 11 | 11 | 11 |
| Hypertensive | | | |
| x̄ | 2.08 | 2.14 | 1.93 |
| s | 0.37 | 0.26 | 0.25 |
| n | 14 | 14 | 13 |
| p | >0.05 | >0.05 | >0.05 |

of plasma (Table XII) increased insignificantly during work in normotensive subjects and returned toward resting values after work ceased. For hypertensive subjects, however, the plasma viscosity decreased to below resting values after work ceased, but this difference was not significant.

The hypertensive group included more obese subjects than the normotensive group, but the difference in weight was not significantly different between the two groups.

In order to see whether these obese subjects could influence the results, the one from the normotensive group and the five from the hypertensive group were excluded and the results were recalculated. There were still significant differences in hematocrit, viscosity, and plasma volume per kilogram of body weight at rest. The reactions of plasma volume, hematocrit, viscosity, and total protein during exercise were unchanged in both the normotensive and hypertensive groups.

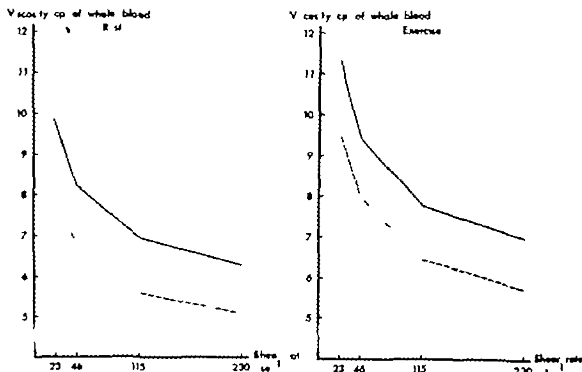



Fig. 3. Viscosity in centipoise of whole blood at rest and during exercise at different shear rates for normotensive (*dashed line*) and hypertensive (*solid line*) subject.

**Discussion**

It was found in a population study of men selected at random that the subjects with diastolic blood pressure ≥ 100 mm. Hg had both increased hematocrit and total serum proteins, even with the obesity factor eliminated. In the present study of two small representative samples from the total population examined, an increased hematocrit, increased blood viscosity, and decreased plasma volume at rest per kilogram of body weight was found in the hypertensive group, as compared with subjects with normal blood pressure. During physical exercise, an increase in both hematocrit and whole blood viscosity and a decrease in plasma volume per kilogram of body weight was found in both groups, whereas the plasma protein level increased only in the hypertensive group. The work load during exercise (600 k.p.m./min.) was similar, as indicated by the identical increases in heart rate in both groups. After work, the values for plasma protein and viscosity returned toward resting values parallel with a decrease in blood pressure and heart rate. In the hypertensive group, however, the hematocrit did not return to resting value during the period of observation.

In an evaluation of the results, it is important to take into consideration the diurnal and seasonal variations in blood volume[4] as well as the sex, age, and body build of the subjects. In our study, all of these factors have been controlled, with the exception of body build. It is well known that hypertensive individuals are more often overweight, as was also the case in this study, but the difference was, however, not significant. Since the controls taken from the total normotensive population were of the same age and sex, it would have been possible to match the controls with the hypertensive subjects and thus eliminate the obesity factor. It was considered, however, that since obesity itself exerts a significant influence on the cardiovascular system, it must be regarded to be fundamentally a pathologic entity to which normal criteria do not apply. Therefore, a random sample from a nor-

motensive population was used instead of a matched group of obese normotensive subjects.

On the basis of our findings it is clear that obesity could not be responsible for the differences between the two groups. In the whole series from 1963, a higher hematocrit and greater total serum proteins were found in the group with diastolic blood pressure $\geq$ 100 mm Hg even when the obese subjects were excluded from the two groups.

The hematocrit levels in the present study are lower than in the 1963 study. The latter study was performed early in the morning, whereas this study was done in the afternoon with the subjects in the recumbent position. In addition to this, different hematocrit methods were used for the two examinations. However, since we have not found any systemic differences between the two methods when used simultaneously, it would appear that the time of day and the fact that in the latter study the subjects were recumbent can account for the differences in hematocrit.

Various findings have been reported for plasma volume in hypertensive subjects. Some reports present normal values,[3,13] with increased plasma volume having been found only in patients with congestive failure.[6] Other observers have reported below normal values for circulating blood volume.[11-14] Of interest is Glazer's finding[9] in 1963 that there was a slight tendency to an elevated hematocrit in the early stages of hypertensive disease, with a decrease evident in the later stages.

Our findings in the normotensive group are in agreement with those of Kaltreider and Meneely,[12] which demonstrated that hemoglobin concentration, serum proteins, and serum viscosity in normal subjects increased during work, and that plasma volume decreased. In their study, resting values were reached within 25 minutes after moderate exercise but not after exhaustive work. The findings were similar in normal subjects and in patients with compensated heart disease. Oehlinger and Buhlmann[8] demonstrated a decreased plasma volume of 10 per cent in sitting work and 3.6 per cent in supine work. The erythrocyte volume was unchanged, resulting in an increased hematocrit. The decreased plasma volume is conceivably due to a movement of fluid into the extravascular space, and most likely in the muscles which increase their volume during work.[17] Concerning the mechanism of the decrease in plasma volume, the effect of vasopressor agents such as noradrenaline and angiotensin is of interest. These agents when injected in moderate pharmacologic doses result in a decreased plasma volume and an increased hematocrit and plasma protein level.[1] Withdrawal of these drugs resulted immediately in a drop in blood pressure below the control level and a rapid transcapillary refilling with increased plasma volume. The mechanism of this response is probably an increased movement of intravascular fluid into the extravascular space due to an increased resistance on the venular side of the capillary bed. It is not unlikely that the decreased plasma volume seen in normal and hypertensive subjects during work is due to such a phenomenon. Recently, Eisenberg and Wolf[4] published data on changes in plasma volume during quiet standing. They found a decrease of 13.2 per cent in a hypertensive group which was significantly greater than the 7.3 per cent decrease seen in the normal group. Mean arterial blood pressures rose in both groups.

Both the increased hematocrit and the increased plasma protein level must influence the viscosity of blood as demonstrated in this study. The hypertensive subjects usually have the type of blood pressure-blood viscosity response at rest that is seen in normal subjects only during work. This is in agreement with the findings of Brod and associates,[2] who found an increased flow of blood in the muscles of hypertensive subjects and the suggestion that the hemodynamic pattern of these patients at rest resembles that of normal subjects during exercise.

*Summary*

Two groups of male subjects of the same age, one with early hypertensive disease and the other normotensive without heart disease, were studied before, during, and after moderate exercise (600 kpm/min). It was found that the hypertensive subjects *at rest* had significantly

higher hematocrit and whole blood viscosity slightly higher plasma protein and slightly lower plasma volume than the normal subjects *During exercise* a significant increase in hematocrit and whole blood viscosity was found in both groups The plasma protein level increased and the plasma volume decreased significantly in the hypertensive group It is suggested that there is an increased leakage of plasma water into the extravascular space in the hypertensive subjects with a decrease in plasma volume and increase in hematocrit viscosity and plasma protein level

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# Treatment of cardiac arrhythmias with beta-adrenergic blocking agents

## Clinical and experimental studies

*Steven Wolfson, M.D.*
*Sanford I. Robbins, B.A.*
*Norman Krasnow, M.D.**
*Brooklyn, N. Y.*

Rapid progress has been made in the past decade in the treatment of cardiac arrhythmias. The introduction of electrical techniques for the conversion or control of many serious arrhythmias has gained rapid acceptance and widespread use. Nevertheless, arrhythmias which have not thus far proved to be amenable to electrical methods of control continue to pose difficult problems for the clinician. During this period few new pharmacologic approaches have proved to be useful.

Knowledge of the influence of catecholamines on the mechanical and electrical properties of the heart has been extended. However, the relationship of catecholamines to clinical arrhythmias, and in particular to arrhythmias provoked by digitalis therapy, remains unclear. The introduction of effective means for blockade of beta adrenergic receptors provides an additional potent tool for study. Pronethalol was introduced by Black and Stephenson[1] in 1962 as an effective beta adrenergic blocking agent, and Vaughan Williams and Sekiya[2] noted that this drug had an antiarrhythmic effect in guinea pigs. A subsequent analogue with similar properties, propranolol, was introduced in 1964.[3]

The purpose of the present study was to evaluate the effects of these two agents in the treatment of clinical and experimentally induced arrhythmias. These agents were shown to be useful drugs in specific circumstances. Like most therapeutic agents, however, they have toxic effects. This study describes several hazards of and contraindications to the administration of pronethalol or propranolol. Animal studies suggest a different mode of action than adrenergic blockade.

## Materials and methods

*Clinical studies.* Twenty-two patients with clinical arrhythmias were included in this series. There were 13 men and 9 women, 30 to 88 years of age. In addition, 5 subjects with normal sinus rhythm were studied. Arrhythmias were studied only if the mechanism was well defined and stable and its relationship to the adminis-

From the Department of Medicine, State University of New York Downstate Medical Center, and the Medical Service, Kings County Hospital Center, Brooklyn, N. Y.

This work was supported by Grant I-361 from the Health Research Council of the City of New York and Grant HE 07952 from the National Heart Institute, Bethesda, Md.

Received for publication Nov. 3, 1965.

*Career Scientist of the Health Research Council of the City of New York. Address: Department of Medicine, State University of New York Downstate Medical Center, 450 Clarkson Ave., Brooklyn, N. Y. 11203.

*Table I. Clinical arrhythmias treated with pronethalol*

| Patient | Sex | Age (yr.) | Clinical diagnosis | Rhythm | Dose (mg.) | Result |
|---|---|---|---|---|---|---|
| E I | M | 59 | Chronic bronchitis | Atrial premature contractions VR 150-180 | 50 | Nodal rhythm VR 75 |
| G K | F | 80 | Hypertensive heart disease CHF digitalis toxicity | NSR VPC (bigeminy) VR 80 | 50 | NSR VR 60 |
| A V | F | 80 | ASHD CHF digitalis toxicity | Atrial fibrillation VPC (bigeminy) VR 100 | 50 | VPC abolished VR 80 |
| I T | M | 72 | Emphysema CHF pneumothorax | Atrial flutter 2:1 conduction VR 130 | 25 | 3-4:1 conduction VR 80 |
| A S | F | 88 | ASHD CHF | AV dissociation with ventricular captures atrial rate 93 VR 50 | 50 | Captures disappeared atrial rate 80 VR 42 |
| F A | F | 61 | RHD | Atrial flutter 2-3:1 conduction VR 110 | 50 | Atrial flutter 4-5:1 conduction VR 70 |
| J S | M | 80 | ASHD CHF digitalis toxicity | Sinus tachycardia wandering atrial pacemaker 1° AV block | 50 | NSR |
| I N | M | 85 | ASHD | Wandering atrial pacemaker VPC VR 80-120 | 100 | No change |
| T M | M | 30 | Atrial septal defect pulmonic stenosis CHF | Atrial flutter 2:1 conduction VR [illegible]0 | 50 | Carotid sinus massage increased block VR 75 |
| J G | F | 60 | RHD mild mitral stenosis | Atrial fibrillation VR 160 | 50 | Atrial fibrillation VR 100 |
| [illegible] W | F | 57 | RHD mitral insufficiency CHF digitalis toxicity | Atrial fibrillation VPC VR 100 | 50 | Atrial fibrillation VPC abolished VR 80 |
| [illegible] I | F | 77 | ASHD CHF | Atrial fibrillation VPC VR 140 | 50 | VPC increased in number VR 170 |
| [illegible] D | M | 45 | RHD mitral insufficiency | Atrial fibrillation VR 140 | 50 | Atrial fibrillation VR 80 |
| W D | M | 60 | ASHD CHF | Atrial flutter 2-3:1 conduction VR 100 | 5† | Atrial flutter 4:1 conduction VR 80 |
| D G | M | 69 | ASHD CHF | Atrial flutter 2:1 conduction VR 130 | 100 | Carotid sinus massage increased block VR 110 |
| A V | M | 46 | RHD mitral valve prosthesis CHF | Atrial fibrillation VPC VR 90 | 90 | No effect |
| A C | M | 57 | RHD severe mitral stenosis pulmonary hypertension CHF | Atrial tachycardia (137/min.) nodal tachycardia AV dissociation VR 107 | 50 | Complete heart block cardiac arrest |
| C R | M | 41 | Hyperthyroidism (controlled) myocarditis (?) | NSR VPC VR 70 | 5† | VPC abolished VR 60 |
| J S | M | 46 | RHD MS AI endocarditis (?) digitalis toxicity | Atrial tachycardia with 1:1 conduction (2:1 with carotid sinus pressure) VR 125 | 5† | Atrial focus slowed to 104 1:1 conduction VR 104 |
| J M | M | 45 | HCVD chronic renal disease with uremia digitalis toxicity | NSR incomplete AV dissociation (nodal rate 72) VPC (multifocal) (total) VR 60 | 5† | Complete AV dissociation (nodal rate 33 with increased aberrant conduction) VPC unchanged VR 60 |

Dose refers to dose of pronethalol [illegible] intravenously [illegible]

†[illegible] (mg.)

Propranolol orally per day (mg.)

*RHD*, Rheumatic heart disease; *ASHD*, Arteriosclerotic heart disease; *HCVD*, Hypertensive cardiovascular disease; *CHF*, Congestive heart failure; *AI*, Aortic insufficiency; *MS*, Mitral stenosis; *VPC*, Ventricular premature contractions; *NSR*, Normal sinus rhythm; *VR*, Ventricular rate per minute.

*Table I Clinical arrhythmias treated with pronethalol*—Cont d

| Patient | Sex | Age (yr) | Clinical diagnosis | Rhythm | Dose (mg) | Result |
|---|---|---|---|---|---|---|
| R R | F | 41 | RHD (mild mitral insufficiency 2 yr after open mitral valvuloplasty) digitalis toxicity | Atrial fibrillation VPC VR 155 | 80 | Atrial fibrillation no VPC VR 65 |
| N F | F | 48 | ASHD acute myocardial infarction shock digitalis toxicity | NSR VPC (bigeminy) VR 120 | 50 | Nodal rhythm A V dissociation VR 75 |

tration of digitalis clear No patient with bronchospasm on auscultation was accepted Congestive heart failure was not a contraindication for the purposes of this acute study

The subjects were given either pronethalol* 50 mg or propranolol 5 mg intravenously over a 5 minute period In 2 cases an additional 50 mg of pronethalol was given intravenously 20 minutes after the initial dose Blood pressure was monitored by cuff frequently Two patients (A V R R ) were given the drug only orally Three patients were subsequently treated with oral pronethalol (300 mg three times daily) or propranolol (30 mg three times daily)

*Animal studies* Twenty four studies were performed on 15 mongrel dogs approximately 15 kilograms in weight anesthetized with intravenous pentobarbital (20 mg per kilogram) A polyethylene catheter was introduced percutaneously into a peripheral vein Electrocardiograms were monitored continuously Ouabain (1 0 mg ) was given intravenously and additional doses (0 25 mg ) were repeated every 10 to 15 minutes until either ventricular tachycardia or multiple ventricular premature contractions were produced The total dose of ouabain required for each animal averaged 65 mg per kilogram When the toxic rhythm had been stabilized for at least 10 minutes pronethalol (mean dose 5 mg per kilogram) was given intravenously over several minutes Electrocardiographic effects occurred within 20 minutes

The animals were allowed to recover for several days from the procedure and then were given reserpine intraperitoneally 0 1 mg per kilogram daily for at least 2 or 3 days This regimen has been shown to lower myocardial (atrial) catechol amines to [3] per cent of control levels [4,5] Ouabain was again given according to the same schedule until toxicity developed Pronethalol (mean dose 3 3 mg per kilogram) was then administered

Ouabain alone was given to 7 animals until ventricular tachycardia developed and they were monitored without further treatment until death

#### Clinical results (Table I)

All patients who responded to pronethalol or propranolol did so within 15 minutes after completion of the infusion One patient complained of nausea several minutes after treatment this was relieved by an intramuscular injection of 200 mg of trimethobenzamide (Tigan Roche) No other side effects were noted The duration of effective blockade averaged 4 hours after intravenous administration and somewhat longer after oral administration

The electrocardiographic changes that followed the administration of pronethalol can be divided into the effects produced upon the sinus node the atria the atrioventricular node and the ventricles Since pronethalol was used in the majority of cases (see Table I) the results will

*[illegible] indebted [illegible] D Alex Sahagian-Edward of [illegible] Laboratories New York for generous supplies of these drugs [illegible] is used in the United States for pronethalol

*Table II Summary of the effects of pronethalol in clinical arrhythmias*

| Rhythm | Number of patients | Result (number of patients) |
|---|---|---|
| Sinus | | |
| NSR | 6 | Slowed (5) |
| | | Developed A V dissociation (1) |
| With A V dissociation | 3 | Slowed (3) |
| Atrial | | |
| Extrasystoles | 2 | Abolished (2) |
| Flutter | 5 | No atrial effect (5) |
| Fibrillation | 5 | No atrial effect (5) |
| Tachycardia | 1 | Atrial rate slowed (1) |
| A V node | | |
| Atrial flutter | 5 | Ventricular rate slowed (5) |
| Atrial fibrillation | 6 | Ventricular rate slowed (6) |
| Dissociation | 3 | Increased block (3) |
| Tachycardia | 1 | Cardiac arrest (1) |
| Ventricular | | |
| Extrasystoles | | |
| Due to digitalis | 6 | Abolished in 5 |
| Not due to digitalis | 4 | Abolished in 1 |

described in terms of this agent although the effects of propranolol were similar

A *Sinus rhythm* Of 8 patients with a sinus mechanism (Table II) the resting sinus rates slowed in 6 by 6 beats per minute Five patients were exercised and had lesser increments in heart rate (10 beats per minute) after pronethalol There was no change in the configuration of the P wave

*B Atrial arrhythmias* Two subjects had multiple atrial premature contractions with ventricular rates of 120 to 150 per minute The premature beats were abolished by pronethalol in each case resulting in a stable nodal rhythm in one case and normal sinus rhythm in the other The resultant ventricular rates averaged 80 per minute In neither case was the arrhythmia thought to be related to digitalis toxicity

Pronethalol had no effect upon the atrial mechanism in 10 patients with atrial flutter or atrial fibrillation (Fig 1)

One patient (J.S.) with atrial tachycardia and 2 1 block due to digitalis had slowing of the ectopic atrial focus and ventricular rate but the 2 1 relationship persisted

*C Atrioventricular node* Pronethalol consistently produced a significant slowing of the ventricular response in atrial fibrillation Initial ventricular rates of 90 to 170 per minute were slowed to 65 to 90 per minute In 4 patients of this group digitalis had failed to slow the ventricular rate despite clinical evidence of toxicity

Pronethalol was also given to 5 patients with atrial flutter Three patients responded with increased A V block and decreased ventricular rates In 2 patients the ventricular rate slowed transiently during carotid sinus massage only after pronethalol The above mentioned effects occurred despite the presence of congestive heart failure severe anoxia (one case) and a spontaneous pneumothorax (one case)

Three patients with complete A V dissociation were treated In 2 patients pronethalol slowed both the atrial and ventricular foci and ventricular captures disappeared (Fig 2) The third subject with rheumatic mitral stenosis very severe pulmonary hypertension and heart failure had a nodal tachycardia a slower atrial tachycardia and A V dissociation (Fig 3) In the attempt to abolish the ectopic tachycardia which was severely compromising cardiac output 50 mg of pronethalol was given over 5 minutes The patient

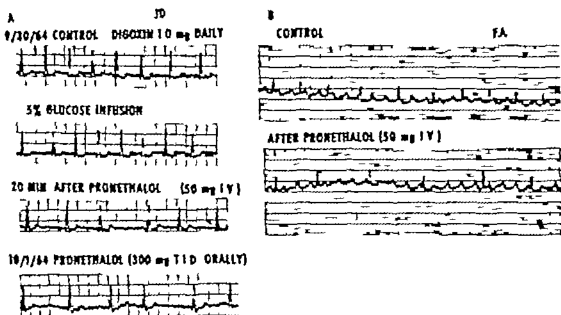



Fig 1 A Atrial fibrillation with rapid ventricular response despite digoxin 1.0 mg daily B Atrial flutter with 2:1 response In each case pronethalol slowed the ventricular rate without effect on the atrial mechanism

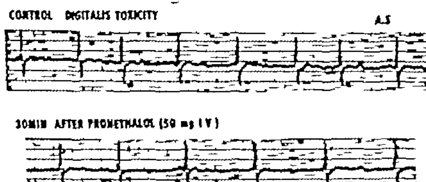



Fig 2 A V dissociation secondary to digitalis intoxication Pronethalol slowed the atrial rate from 93 to 80 per minute the ventricular rate from 50 to 47 per minute and abolished ventricular captures (C)

developed complete heart block with an idioventricular rhythm as the infusion was completed and within 2 minutes cardiac arrest supervened Rapid intravenous administration of isoproterenol and intracardiac epinephrine as well as the usual resuscitative measures were unable to reverse the arrest

*D Ventricular effects* No changes in QRS configuration or duration were noted

Pronethalol was successful in 5 of 6 patients in abolishing ventricular extrasystoles which were considered to be due to digitalis toxicity (Fig 4) but one of these subjects developed A V dissociation Of 4 patients with frequent ventricular premature beats unrelated to digitalis one responded to pronethalol One of the refractory patients (E F ) presented with atrial fibrillation a rapid ventricular response and frequent ventricular ectopic beats She had received 1.6 mg of lanatoside C Pronethalol slowed the ventricular rate but the extrasystoles increased in frequency She was then treated with additional lanatoside C with further slowing

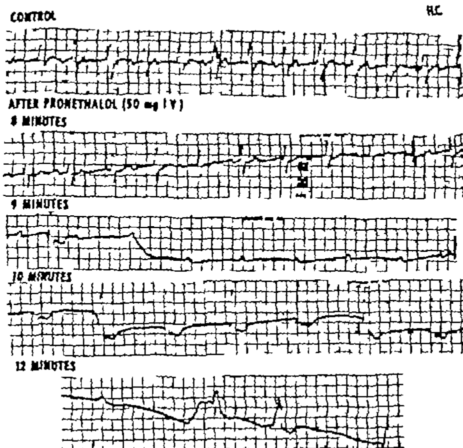



Fig. 3. A-V dissociation with sinus and nodal tachycardia in a patient with mitral stenosis and severe pulmonary hypertension. Cardiac arrest followed progressive slowing of the nodal, sinus and ventricular pacemakers.

of the ventricular rate and abolition of the extra beats.

**Animal studies (Table III)**

Eight dogs had 11 episodes of ouabain-induced ventricular arrhythmia treated with pronethalol. In 7 of these episodes pronethalol caused reversion to a supraventricular tachycardia.

When 6 of these animals had been pretreated with reserpine they also developed ventricular tachycardia after ouabain. All 6 episodes of ventricular tachycardia were successfully converted to a supraventricular mechanism (although in 2 cases the result was only transient) (Fig. 5). In this small group of animals there was no increase in the toxic dose of ouabain after reserpine.

None of the animals succumbed to ouabain toxicity when pronethalol was given, even when the ventricular arrhythmia did not revert to a sinus mechanism during the 3 hour period of observation. By contrast, 7 animals were given ouabain until toxicity developed but pronethalol was withheld. All died of arrhythmia: either ventricular standstill or fibrillation.

**Discussion**

Sympathomimetic agents have found wide clinical application both for their potentiation of cardiac contractility and their stimulatory effect on pacemaker sites.[8] Adrenergic stimulation of the heart produces[7,[illegible]] increased rhythmicity of the sinus node, a shortened refractory period in atrial muscle, more rapid atrioventricular conduction and enhanced activity of idioventricular pacemakers. These effects are thought to be subserved by beta adrenergic receptors within the heart.[[illegible]]

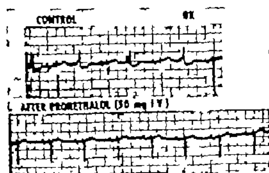



Fig 4 Reversal of ventricular bigeminy due to digitalis toxicity Note also slowing of sinus rate

Hoffman[7] suggests that the increased rate of diastolic depolarization of pacemaker cell membranes is the cellular basis for increased rhythmicity and automaticity He considers that all pacemaker sites defined as automatic cells are located within the conduction system Wallace and Sarnoff[1] have shown that conduction in Purkinje tissue and ventricular myocardium is not significantly affected by sympathetic nerve stimulation

Given this broad spectrum of activity it might prove to be valuable in certain circumstances to minimize sympathetic influences upon the heart Until recent years however selective beta adrenergic blockade has not been possible The dichloro derivative of isoproterenol offered promise in this direction but further experience showed that it has a significant intrinsic sympathomimetic effect[11] In 1962 pronethalol the naphthyl derivative of isoproterenol was introduced[1] and proved to be an effective antagonist of the beta adrenergic catecholamines It prevented the chronotropic and inotropic effects of intravenous isoproterenol and stellate ganglion stimulation in both animals and man[1 12] In addition it produced a bradycardia in acutely sympathectomized animals and thus is thought to be effective against myocardial stores of catecholamines However 11 per cent of rats given pronethalol in high doses for prolonged periods of time developed lymphosarcomas Propranolol a noncarcinogenic analogue with pharmacologic properties similar to pronethalol has now replaced pronethalol[8]

## Arrhythmias

Evidence has been presented which suggests that pronethalol may be a potent antiarrhythmic agent The data demonstrate effects of beta adrenergic blockade at several levels of the pacemaker and conduction system of the heart

The 5 patients with normal sinus rhythm showed slowing of cardiac rate both at rest and exercise rates This result is consistent with reported studies utilizing both pronethalol and catecholamine-depleting agents in animal and human subjects[1 12, 8] One patient with complete A V

*Table III Reversal of ouabain induced ventricular tachycardia in the dog by pronethalol before and after reserpine pretreatment*

| Number of animals | Ouabain mean dose (mg ) | Arrhythmia | Pronethalol mean dose (range) (mg ) | Result | |
|---|---|---|---|---|---|
| Without reserpine | | | | | |
| 11 | 1 3 | Ventricular tachycardia | 110 (25 180) | Supraventricular tachycardia | 7† |
| | | | | Ventricular tachycardia | 4 |
| With reserpine pretreatment | | | | | |
| 6 | 1 2 | Ventricular tachycardia | 65 (25 160) | Supraventricular tachycardia | 6 |
| | | | | Ventricular tachycardia | 0 |

1 dog ... with equivalent dose ... of pronethalol 1
†Transient in 2

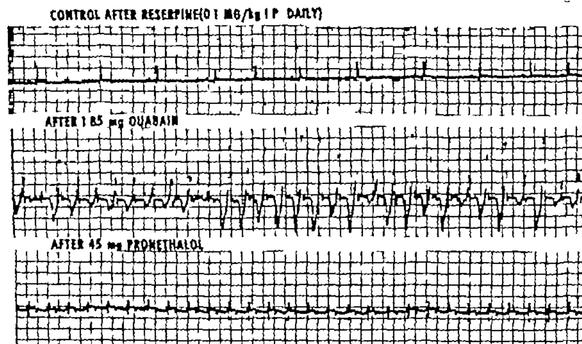



Fig. 5. Ouabain-induced ventricular tachycardia in the reserpinized dog. Pronethalol caused reversion to a sinus mechanism.

dissociation had slowing of both the sinus and ventricular rates, as did dogs with surgical heart block treated with reserpine by Roberts and Modell.[19]

There was no change in the atrial rate of atrial flutter, consistent with reports of others.[11,25] Atrial premature contractions, however, have been decreased in number. Reversal of paroxysmal atrial tachycardia with block caused by digitalis toxicity has been reported,[14] although in the present case only slowing of the ectopic focus was achieved.

Pronethalol consistently slowed conduction across the A-V node, as evidenced by slowing of the ventricular rate in atrial flutter and fibrillation and development of A-V dissociation. This effect is consistent with the results of experimental studies. Conduction through the A-V node is increased by sympathetic nerve stimulation[11,19,27] and decreased by acute or chronic sympathectomy or treatment with reserpine.[27] Reserpine has also been shown to increase A-V block in patients with atrial fibrillation.[1]

The results thus far suggest that pronethalol may inhibit ventricular extrasystoles particularly when caused by digitalis toxicity. This has been shown by others.[3,11,14,15,27] Adrenergic blockade by other means can also prevent or reverse ventricular irritability related to digitalis toxicity,[4,5,11] but the fundamental relationship between digitalis and catecholamines is unclear. Tanz[21,28,29] reported abolition of the positive inotropic effect of ouabain upon cat papillary muscles when the strips were pretreated with dichloroisoproterenol, reserpine, or guanethidine. Other workers, using diverse means of inhibiting catecholamine activity, have found that pronethalol,[1] reserpine,[22,17] acute or chronic sympathectomy, total cardiac denervation,[23] or βTM 10[5] do not inhibit the positive inotropic action of digitalis preparations.

The present studies in animals indicate that the ventricular irritability caused by digitalis is not solely related to adrenergic stimuli, since the dogs pretreated with reserpine also developed ventricular ectopic rhythms in response to ouabain. Similarly, digitalis toxicity may be observed in the totally denervated heart[23] or the reserpinized cat papillary muscle.[29]

Moreover the present data show that pronethalol reverses ouabain induced ventricular tachycardia even in reserpine pretreated dogs suggesting a mechanism of action other than beta blockade.* Lucchesi[7] and Somani and Lum[44] also concluded from time dose relationships and the effects on action potentials that pronethalol has a nonspecific action which may be responsible for its antiarrhythmic effect.

### Clinical indications and contraindications

The indications for the use of pronethalol in cardiac arrhythmias appear thus far to be limited but specific. The most useful effect has been the slowing of the ventricular rate in atrial fibrillation or flutter when this was not otherwise possible by large or toxic doses of digitalis. It also produces a rapid and relatively prolonged reversal of increased ventricular irritability especially when caused by digitalis. This may be particularly useful when the administration of potassium is not effective or is contraindicated. Unlike calcium versenate pronethalol need not be infused repeatedly. On the other hand the underlying congestive failure for which digitalis was prescribed may be aggravated by the prolonged use of the adrenergic blockade.

The only death reported due to pronethalol occurred in the present series although we are aware of several others two instances in subjects with congenital heart disease.[42]

Pronethalol is contraindicated in the presence of bradycardia since the rates of all pacemaker sites are lowered by the drug. Complete A V dissociation or a high degree of A V block would also appear to preclude the use of pronethalol since the higher pacemakers may be suppressed along with the lower ones. The hazard is analogous to the use of quinidine in this situation.

No signs of increased pulmonary congestion were encountered in this study in 14 patients with congestive heart failure treated with a single intravenous dose of pronethalol. Although the cardiac output of normal subjects is not decreased after guanethidine,[24] reserpine,[17] sympathectomy,[17] or pronethalol,[1, 33, 39] subjects with congestive heart failure may be dependent upon a cathecholamine stimulus for adequate myocardial function and thus may react to long term administration of pronethalol with a worsening of their congestive heart failure.[11, 40, 41] Until additional data are available therefore the presence of moderate to severe congestive heart failure should be considered to be a relative contraindication to the chronic administration of pronethalol. Perhaps an exception would be the case in which a rapid ventricular rate is contributing to the failure.

Beta adrenergic blockade may cause a fall in venous return since it has been shown that beta receptors in the peripheral venous bed subserve venoconstriction.[4-] This suggests that pronethalol should be used with caution in conditions such as pulmonary hypertension and congestive heart failure in which an adequate venous return is essential for maintaining cardiac output.

In addition the drug blocks the bronchodilator effects of the catecholamines and its use should be avoided when bronchospasm is present.

Finally a potential hazard exists in stenosis of the semilunar valves since experimentally catecholamines may be required to maintain adequate velocity or force of ventricular contraction.[44]

### Summary

Twenty seven subjects with various cardiac rhythms were treated with intravenous pronethalol or propranolol. Slowed sinus rhythmicity decreased A V node conduction and decreased ventricular premature contractions (particularly if caused by digitalis) were observed. One death occurred in a patient with A V dissociation severe pulmonary hypertension and congestive heart failure. No other significant side effects were seen.

These two drugs are considered to be quite useful in controlling ventricular responses to atrial flutter or fibrillation

*It is possible that the small residual stores of catecholamines not removed by reserpine (approximately 2 per cent)[illegible] might exert [illegible] an effect or trigger for digitalis-induced arrhythmias. In this sense it is difficult to exclude the possibility that pronethalol may produce its effect by beta blockade alone.

and in certain cases of ventricular arrhythmias. They are rapid acting and potent. Their use may be hazardous when bradycardia or A-V dissociation is present or if the arrhythmia is complicated by severe congestive heart failure or bronchospastic pulmonary disease.

Data in animals confirm the reversal of digitalis toxicity and suggest a mechanism of action in addition to beta adrenergic blockade.

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# A pathologic-arteriographic correlation of renal arterial disease

*Lawrence J McCormack M D**
*Eugene F Poutasse M D***
*Thomas F Meaney M D*
*Thomas J Noto Jr M D****
*Harriet P Dustan M D*
*Cleveland Ohio*

Various types of lesions produce renal arterial stenosis Although atherosclerosis is the most common there are other lesions that are being recognized with increasing frequency Our early experience suggested that most disease that was not atherosclerotic represented fibromuscular hyperplasia[1] following the original report other types were identified and now we know that fibromuscular hyperplasia occurs less frequently than types with *dominance of fibrous and absence of* muscular hyperplasia Furthermore continuing experience has shown that these renal arterial diseases may have distinctive arteriographic features that in themselves can be diagnostic when the length of renal artery affected is sufficient for the entire pattern to be displayed

This report describes the pathologic and arteriographic characteristics of renal arterial lesions in 97 patients most of whom were examined before 1963 On the *basis of microscopic features* the lesions were classified according to their primary locations in the vessel walls There were two types of lesions primarily of the intima atherosclerosis and intimal fibroplasia and three types predominantly affecting the media medial fibroplasia with aneurysm fibromuscular hyperplasia and subadventitial fibroplasia Only patients who had total arterial resections were included

## Materials and methods

Arterial segments were obtained at the time of operation in 94 patients who were operated upon for relief of diastolic hypertension and at autopsy in the other 3 After the specimens were treated by the standard fixing procedures either a modified Zenker's or formalin appropriate sections were obtained depending on the nature of the lesion When long segments of an artery were affected longitudinal sections often provided the clearest picture *of the pathologic features* When an artery

From the Division of Pathology the Department of Urology the Division of Radiology and the Division of Research The Cleveland Clinic Foundation Cleveland Ohio

This study was supported in part by Grant No [illegible] from the National Heart Institute Bethesda Md and Grant No [illegible] from the United States Public Health Service Washington D C

Received for publication [illegible]

*Address Division of Pathology Cleveland Clinic 2020 East 93rd St Cleveland Ohio 44106
**Formerly member of the staff Department of Urology Present address 804 Medical Tower Norfolk Va
***Formerly Special Fellow in Cardiology Present address 1333 South Miami Ave Miami Fla

was completely occluded, cross sections permitted ready recognition of the site of the original lumen. Sections were stained with the usual hematoxylin and eosin stains and for connective tissue with Mallory Heidenhain, Masson trichrome, Verhoeff Van Gieson, Gomori elastic, and toluidine blue and Rinehart Abul Haj stains. Sudan IV was used on selected frozen sections from unprocessed blocks.

Renal arteriography had been performed in each patient; about three fourths of the arteriograms had been obtained by translumbar aortic injection of contrast medium[3] and the rest by selective renal arterial injection.[4]

**Results**

The number of patients in each diagnostic group, as well as the age and sex distributions, are shown in Table I.

*Atherosclerosis* was present in 30 patients, 25 men and 5 women, ranging in age from 28 to 68 years. Two types of lesions were found. In about one third of the cases there was a circumferential atheroma with areas of accumulation of lipid and often focal calcification (Fig. 1). In the larger group, the intima was thickened by an eccentric fibrous plaque often composed primarily of collagen. However, Sudan IV staining of frozen sections showed some deposition of lipid, permitting the designation of the lesion as an "old" atheroma. With both types of lesions, two complicating features were sometimes found—thrombosis and dissecting hematoma originating distal to the point of maximal narrowing. Both types usually produced complete arterial occlusion.

Renal arteriography showed these lesions to be predominantly in the first 2 cm. of the renal artery (Fig. 2). Bilateral disease occurred in 12 of the 30 patients. The stenosis often appeared to be asymmetrical, reflecting the gross and microscopic findings of localized formation of plaques. Poststenotic dilatation was frequent. In some patients, complete occlusion had occurred because of either thrombosis or hematoma, and only a short stub of renal artery was clearly visible (Fig. 3).

*Intimal fibroplasia* occurred in 14 patients, 9 males and 5 females, whose ages ranged from 18 months to 48 years. Microscopically, this fibroplasia was found to be a lesion of the intima and *elastica interna*. The intimal hyperplasia appeared as a segmental circumferential accumulation of cellular collagen without a lipid component (Fig. 4). The collagen was somewhat primitive; at times it stained metachromatically with toluidine blue and positively with colloidal iron. There are possibly two types of this lesion because that found in youthful patients seemed to be different from that in the adults. In the former, the *elastica interna* was often reduplicated and there was slight disorganization of the media; in contrast, in the adult variety these aberrations were not present. In some specimens the collagen was closely applied to large folds of the *elastica*, as though arterial spasm had

*Table I. Age and sex distributions in renal arterial diseases in 97 patients*

| Site and type of lesion | Total number | Males | | Females | |
|---|---|---|---|---|---|
| | | Number | Age range (yr.) | Number | Age range (yr.) |
| Intima | | | | | |
| Atherosclerosis | 30 | 25 | 8–68 | 5 | 45–65 |
| Intimal fibroplasia | 14 | 9 | 1.5–47 | 5 | 33–48 |
| Media | | | | | |
| Medial fibroplasia | 15 | 3 | 41–58 | 12 | 30–59 |
| Fibromuscular hyperplasia | 7 | 5 | 15–45 | 2 | 10–17 |
| Subadventitial fibroplasia | 31 | 5 | 17–40 | 26 | 14–48 |
| Grand total | 97 | | | | |



Fig 1 A severe degree of concentric atherosclerosis complicated by thrombosis is present Hematoxylin and eosin stain magnification ×12



Fig Selective renal arteriogram showing asymmetrical narrowing by an atherosclerotic plaque in the first portion of the artery with poststenotic dilatation Presence of this plaque was confirmed at operation when an endarterectomy was performed

occurred and the artery had been fixed in that state by the accumulation of collagen Often a segment of the internal elastic membrane distal to the stenosis had completely disappeared resulting in either of two types of aneurysms One a dissecting aneurysm (intramural hematoma) occurred proximal as well as distal to the stenosis and in the proximal extension overrode the area of stenosis (Fig 5) The other was an aneurysmal dilatation due to destruction of almost the entire vessel wall and only the adventitia provided continuity (Fig 6)

*The arteriographic features seemed to* depend on the integrity of the internal elastic membrane When the *elastica* was intact fibroplasia produced a symmetrical narrowing of the main renal artery or the primary branches with poststenotic dilatation *(Fig 7) When it was disrupted* the resultant aneurysm appeared as a dilated segment (Fig 8) Sometimes the stenosis was not apparent because of proximal dissection and the only arteriographic abnormality was an irregularly dilated artery It was the irregularity that distinguished this dilatation from the poststenotic type The dissecting aneurysm



Fig 3 Translumbar aortogram and renal arteriogram in a patient with atherosclerosis in the first portion of each renal artery On the right there is slight irregularity in the outline of the vessel On the left the arterial outline ends abruptly probably because complete or nearly complete occlusion had been produced by the thrombosis that was found in the segment removed at the time of nephrectomy The faint arterial filling distally suggests either that this artery was not completely occluded by the thrombus or that collateral circulation was adequate to produce faint opacification



Fig. 4. Initial fibroplasia in an infant. Photomicrograph of cross section of renal artery close to aorta. The subintimal collagenous zone (*arrow*) superimposed on the internal elastic membrane is extensive. The elastic fibers seen in the media in this section occur normally in the first portion of the renal artery as an extension of the medial elastic fibers of the aorta. Verhoeff-Van Gieson stain; magnification ×55.



Fig. 6. A photomicrograph of a renal artery distal to a stenosis produced by intimal fibroplasia. There is almost complete destruction of the arterial wall (*top*) and only the external elastic membrane is intact. Intimal fibroplasia is seen superimposed on remnants of the internal elastic membrane (right hand and lower portions of the section). Verhoeff-Van Gieson stain; magnification ×36.

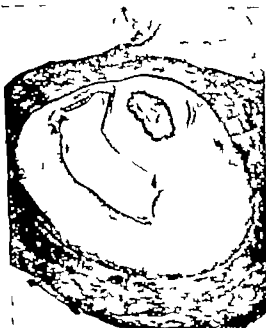


Fig. 5. Intimal fibroplasia in a polar branch of the renal artery. The large channel is part of a dissecting hematoma. Verhoeff-Van Gieson stain; magnification ×18.



Fig. 7. Translumbar arteriogram of intimal fibroplasia of the superior branch of the left renal artery. The arrow indicates poststenotic dilatation of secondary branches. The stenosis is just proximal part of it overlying the large arterial branch to the mid portion of the kidney. At operation the upper pole of the kidney was removed. On microscopic examination the internal elastic membrane of the arterial branch was intact.



Fig 8 Translumbar renal arteriogram of intimal fibroplasia of the left renal artery with disrupted internal elastic membrane and aneurysmal not poststenotic dilatation There are two and perhaps three areas of aneurysmal dilatation the proximal one overlies and obscures the stenosis

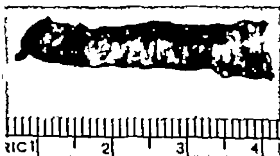



Fig 9 Photograph of longitudinal hemisection of renal artery showing corrugations and orifices of aneurysms in medial fibroplasia

could not be differentiated from aneurysmal dilatation and appeared only as an irregularly dilated segment

*Medial fibroplasia with aneurysms* is the lesion that produces the string of beads arteriogram usually considered to be characteristic of fibromuscular hyperplasia[4] It was present in 15 patients 12 women who ranged in age from 30 to 59 years and 3 men who were 41 to 58 years of age Grossly the artery was irregularly dilated the dilatations on longitudinal sections representing aneurysmal outpouchings (Fig 9) Microscopically the lesion was often seen in long segments of the renal



Fig 10 Longitudinal section of medial fibroplasia showing severity and variability of destruction of arterial wall Verhoeff Van Gieson stain magnification X20

artery and sometimes in the primary branches In some areas there was destruction of the intima *elastica interna* and the media producing aneurysms These areas alternated with segments of media in which the smooth muscle and fine elastic digitations were lost and replaced by collagen (Fig 10) much as can be seen in aging muscular arteries Intimal fibroplasia was sometimes present in areas in which the vessel wall was still intact and seemed to be capable of producing stenosis

On arteriograms the lesions often were bilateral usually the first centimeter of the renal artery was spared but in some cases the entire length distal to that including the primary branches was affected The beading was produced by aneurysmal segments (the beads ) joined by short segments which sometimes did not appear to be narrowed (Fig 11) The characteristic feature of the beads was the aneurysmal nature since almost without exception their diameters exceeded that of the apparently unaffected proximal



Fig 11 Selective right renal arteriogram of medial fibroplasia The arrows indicate the apparent proximal and distal limits of the disease The characteristic feature is the aneurysmal dilatation which are wider than the apparently unaffected proximal artery (cf arteriogram of subadventitial fibroplasia)



Fig 12 String-of-bead arteriogram of medial fibroplasia of the left renal artery (between the arrows) Regions of stenosis are apparent and these separate areas of aneurysmal dilatation which are of greater diameter than the seemingly unaffected proximal artery

artery (Fig 12) In most patients short segments of stenosis were present however the aneurysmal beading permitted a correct anatomic diagnosis to be made from the arteriograms This retrospective study did not permit a comparison of stenotic areas seen on arteriograms with the presence of intimal fibroplasia and it may be that even in a prospective study such a comparison would not be feasible

*Fibromuscular hyperplasia* was present in only 7 patients Three of these 1 boy and 2 girls ranged in age from 10 to 17 years the other 4 were men from 29 to 45 years of age In the younger patients the hyperplasia occurred as a segmental concentric stenosing lesion composed of an unorganized mixture of smooth muscle and fibrous tissue The quantities of the two components were variable in the case originally described[1,4] the two seemed to be equal in amount (Fig 13) but in the 2 later cases muscular tissue predominated In the 4 men an additional feature was disruption of the *elastica interna* distal to the stenosis with formation of a dissecting aneurysm

The arteriographic findings indicated either stenosis or aneurysm In the 3 young patients the internal elastic membrane

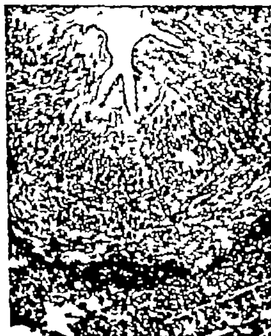


Fig 13 Cross section of fibromuscular hyperplasia showing medial thickening because of increased amount of fibrous and muscle tissue The internal elastic membrane is absent Verhoeff Van Gieson stain magnification X100



Fig 14 Arteriogram showing severe stenoses of the orifices of both renal arteries produced by fibromuscular hyperplasia Characteristically symmetrical poststenotic dilatation is seen on the left as well as coarctation of the abdominal aorta The large inferior mesenteric artery may have been furnishing collateral blood supply to the left kidney

was intact and the arteriograms showed a symmetrical stenosis with poststenotic dilatation In 1 of these the lesion occurred in a large primary branch just beyond its origin In 2 stenoses of the orifice of the main renal artery were present one bilateral (Fig 14) and the other unilateral In these 3 patients there was narrowing (coarctation) of the abdominal aorta which extended from above the origin of the renal arteries to or close to the aortic bifurcation In the 4 older patients dissection had occurred which obscured the stenosis In each of 3 the artery was irregularly dilated and the dilatation was indistinguishable from that found in intimal fibroplasia In 1 the translumbar arteriogram appeared to be normal but at operation the posterior branch was found to be completely obstructed by a dissecting aneurysm containing a thrombus Clearly an oblique arteriogram would have permitted preoperative recognition of the occlusion of the arterial branch because in the nephrogram phase of the arteriogram the posterior segment would not have been opacified

*Subadventitial fibroplasia* was present in 31 patients 5 males and 26 females ranging in age from 14 to 28 years The lesion was made up of dense collagen enveloping the renal artery for varying lengths up to as much as 2 cm This collagenous material was in the outer portion of media (Fig 15) often replacing it irregularly and causing much disorganization of the muscular coat Islands of smooth muscle cells were entrapped in the dense fibrotic tissue The *elastica interna* was intact and occasionally segments of intimal fibroplasia were present but these were insignificant compared to the amount of peripheral fibrosis Special staining techniques highlighted the changes and showed that the external elastic membrane was also affected and that the lesion therefore was not completely subadventitial in location (Fig 16)

Arteriography showed subadventitial fibroplasia to be a severely stenosing lesion primarily of the right renal artery The right side was affected in 18 patients the left side in 7 and both sides in 6 The length of artery involved varied from a sharply localized area (Fig 17) to the distal two thirds of the main trunk branches often were affected Disease of the main renal artery was found in 27

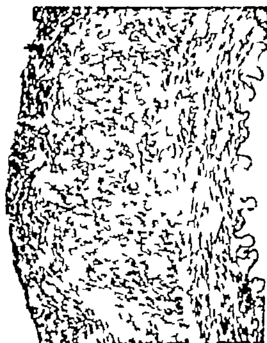


Fig 15 Photomicrograph of subadventitial fibroplasia showing the presence of a dense sclerotic band between remnants of media and adventitia Hematoxylin-eosin stain magnification ×80



Fig. 16. Photomicrograph of a cross section of subadventitial fibroplasia showing dense collagen replacing most of the external elastic membrane and the media. The thickness of the collagen is indicated by the arrow. Verhoeff-Van Gieson stain, magnification ×60.



Fig. 18. Subadventitial fibroplasia of the right renal artery (between arrows). The stenosis is severe and accompanied by prominent collateral blood supply. Characteristically the stenosis is variable giving the impression of beading; however, the beads are not aneurysmal (cf. medial fibroplasia, Figs. 11 and 12).



Fig. 17. Right renal arteriogram showing a sharply localized stenosis (arrow) of the lower right renal artery produced by subadventitial fibroplasia.

patients and in 13 of these it extended into the branches also. Lesions of the branches without involvement of the main trunk occurred in 2 patients. As for the other 2 patients, each had two renal arteries supplying the right kidney; one artery was normal and the other stenotic.

Within the affected segments of main arteries, the stenosis was variably severe, with regions of intense narrowing alternating with those of lesser stenosis (Fig. 18). This gave the appearance of beading. This beading was not aneurysmal as in medial fibroplasia because the width of the beads was less than that of the unaffected proximal artery. Collateral blood channels bypassing the stenosis occurred frequently, perhaps indicating the severity of stenosis.

## Discussion

Understanding of the pathology of renal arterial diseases has been greatly aided by using a combination of tissue fixing and sectioning techniques to obtain a three-dimensional concept of each type of lesion. When sequential cross sections are used,

as in the study of aneurysms associated with intimal fibroplasia or fibromuscular hyperplasia it is best to fix the entire arterial segment before cutting the sections. Longitudinal sections are helpful in examining medial fibroplasia and to obtain these the fresh arterial segment should be opened longitudinally before careful flat fixation. After fixation parallel sections can be easily cut. This type of fixation and sectioning should not be used for examination of the occluded artery because in this situation it does not permit ready identification of the original anatomic landmarks. Important information can often be obtained from study both of cross sections and of longitudinal sections of different parts of the same artery.

Our first reports[1,4] of the pathology of renal arterial disease described findings in a small number of arteries. With more experience it became apparent that the original designation of nonatherosclerotic lesions as fibromuscular hyperplasia and segmental mural fibrosis did not adequately describe the variety of changes observed. The present classification takes these varieties into consideration and is accordingly based on the predominant microscopic features and their primary locations in the vessel walls. This classification is similar to that described by Hunt and associates[7] with the advantage that a rather close pathologic-arteriographic correlation is possible.

During the years of growing interest in renal arterial disease diagnosis of atherosclerotic stenosis did not present a problem. The gross and microscopic pathology was readily recognized and the location of stenotic lesions predominantly at the orifice permitted arteriographic diagnosis even before techniques were available for visualizing the entire renal arterial supply.[8,10] Continuing experience has shown that these lesions occur more frequently in men than in women and at the time of life when symptoms of atherosclerosis appear. The plaque is almost always at the orifice or in the first 2 cm. of the renal artery. It usually produces an asymmetrical stenosis that often is accompanied by poststenotic dilatation. For preoperative diagnosis knowledge of the patient's age and sex as well as the site and arteriographic appearance of the lesion permits a high degree of accuracy.

Recognition of the various types of renal arterial disease that are not atherosclerotic has evolved slowly. The first report seems to be that of Leadbetter and Burkland[11] in 1938 which described a cure of hypertension by nephrectomy in a 5-year-old boy. The excised renal artery had been obstructed by a sessile mass of muscular tissue covered by normal-appearing internal elastic membrane and intima. The arterial wall itself seemed to be normal except at the origin of the mass.

Development of renal arteriography in the nineteen fifties reawakened interest in occlusive renal arterial disease. Some early reports described fibrosing lesions: one lesion was found in the outer media[12] and the rest were considered to be located in the intima.[13,14] One case at our institution[14] was later reclassified as fibromuscular hyperplasia.[1,4] A 1958 abstract by McCormack, Hazard and Poutasse[1] divided the nonatheromatous lesions into fibromuscular hyperplasia and segmental mural scarring (the latter is now called subadventitial fibroplasia). Later Wylie and associates[17,18] and Wellington[19] used the term fibromuscular hyperplasia to include all types of lesions that are not atherosclerotic.

The results of the study reported here indicate that fibroplasia is the dominant feature of most fibrosing disease and that muscular hyperplasia is unusual. Although we reserve the term *fibromuscular hyperplasia* for the uncommon lesions with increased amounts of both fibrous and muscular tissue the term *fibroplasia* seems to be a better description for most of the lesions that are not atherosclerotic. Furthermore the designation of the primary site of the fibroplasia (i.e. intimal medial subadventitial) is helpful because of associated anatomic and clinical features. This classification of nonatherosclerotic renal arterial disease although useful diagnostically gives no indication of etiological factors.

The youthful type of intimal fibroplasia can affect not only the renal arteries but also the adjacent aorta and orifices of splenic celiac and hepatic arteries.[14] Brust and associates[14] have pointed out that aortic involvement can produce long segments of abdominal coarctation. In our

experience this has not caused arterial pressure gradients large enough to suggest a clinical diagnosis of aortic coarctation. The relationship between the changes in various age groups is not clear but it is the dissolution of the elastic membrane which produces aneurysms and accounts for the characteristic appearance on arteriograms. The aneurysmal dilatations tend to be larger and longer than those accompanying medial fibroplasia.

Medial fibroplasia is also not confined to the renal artery. Palubinskas and Ripley[8] recently reported a celiac arterial lesion and we have observed the typical arteriographic features in the carotid arteries of a woman with bilateral renal arterial lesions. In our experience, as in that of Wellington[11] and of Hunt and associates,[7] medial fibroplasia was present much more frequently in women than in men and in the middle decades of life; often it was bilateral. On arteriograms it is distinguishable from subadventitial fibroplasia by the presence of aneurysms instead of areas of variably severe stenosis.

Subadventitial fibroplasia has been found in younger women than has medial fibroplasia. Curiously, it is primarily a lesion of the right renal artery. Kaufman, Hanafee, and Maxwell[1] suggested that ptosis of the right kidney is in some way an etiological factor, but in patients whom we have studied ptosis did not seem to be an important feature. The affected kidney usually was considerably shorter than its mate, indicative of the severity of the stenosis; the severity is further suggested by the abundant collateral circulation that is readily apparent. Although on the arteriograms there is evidence of beading at the renal artery, this is an indication of varying degrees of stenosis and not of the presence of aneurysms.

There is a possibility that two types of fibromuscular hyperplasia exist—primary and secondary. The primary type would be represented by the fibromuscular hyperplasia with intact *elastica interna*, such as we found in each of the 3 patients from 10 to 15 years of age. In the secondary type the hyperplasia would develop as a reaction to a dissecting hematoma of unknown cause.

We have not seen the periarterial fibrosis reported by Hunt and associates[7] and by Wood and Borges. Neither have we seen the inflammatory aortic and renal arterial lesions reported from South Africa[12] and Singapore.[4]

The classification presented here provides a broader description of renal arterial lesions than has been possible in the past. It should permit accumulation of knowledge about the pathogenesis and natural history of these arterial diseases because they can now be recognized by arteriography. Furthermore, this classification may help in selecting the appropriate operative procedures for each type of lesion, thereby improving the results of surgical treatment for hypertension associated with renal arterial diseases.

## Summary

A study of the microscopic features of occlusive renal arterial lesions in 97 patients has shown the advantage of classifying these diseases according to their primary locations in the arterial wall and the types of tissue they comprise. Two lesions were primarily intimal, atherosclerosis and intimal fibroplasia, and three were predominantly medial: medial fibroplasia, fibromuscular hyperplasia, and subadventitial fibroplasia. This classification permitted a close correlation with renal arteriographic features.

Atherosclerotic lesions were either circumferential or eccentric plaques, sometimes complicated by thrombosis or dissecting aneurysm. They occurred predominantly in men. Arteriograms showed stenosis of the orifice with poststenotic dilatation; the presence of thrombosis or dissecting aneurysm was usually indicated by complete obliteration.

Intimal fibroplasia was characterized by fibrous intimal hyperplasia associated at times with disruption of the internal elastic membrane. Arteriographic features depended on the condition of this membrane; when it was disrupted, an aneurysm formed, producing an irregularly dilated artery.

Medial fibroplasia with aneurysms produced the string-of-beads arteriogram previously attributed to fibromuscular hyperplasia. The beads were aneurysms that developed because segments of the arterial wall were absent, permitting focal dilatations. These thin segments alter

nated with areas in which the media had been largely replaced by collagen Muscular hyperplasia was not present

Fibromuscular hyperplasia was an uncommon lesion resulting from increased amounts of fibrous and muscular tissue it was sometimes accompanied by disruption of the internal elastic membrane Arteriograms showed either symmetrical stenosis or when the internal elastic membrane was disrupted an irregularly dilated artery We could find no arteriographic features that would differentiate this lesion from intimal fibroplasia

Subadventitial fibroplasia was characterized by dense collagenous thickening of the outer media irregularly replacing the muscular layer it affected long segments of the renal artery The arteriographic appearance was that of a severely stenosing lesion with regions of intense stenosis alternating with regions of lesser narrowing This lesion has also been called fibromuscular hyperplasia because the variably severe stenosis produces an irregular arterial outline that suggests beading This study shows subadventitial fibroplasia to be distinct from fibromuscular hyperplasia as well as from medial fibroplasia which produces the string of beads arteriogram

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# Preoperative and postoperative electrocardiogram in complete transposition of the great vessels

*George H. Khoury, M.D.**
*Reda M. Shaker, M.D.*
*Rodney S. Fowler, M.D.*
*John D. Keith, M.D.*
*Toronto, Canada*

With the recent advances in the surgical treatment of complete transposition of the great vessels[1], re-evaluation of the electrocardiogram in this condition before and after creation of an atrial septal defect and after total correction with the Mustard procedure seemed to be warranted in order to examine the effect of these two different surgical procedures on the electrical activity of the heart.

Several authors[2-7] have described the electrocardiogram in complete transposition of the great vessels in relation to the underlying pathology. Recently, Shaher and associates[8] referred to the hemodynamic findings in their cases to explain the different electrocardiographic findings. It is the purpose of this report to present the preoperative and postoperative findings in 30 cases of complete transposition of the great vessels.

## Methods and material

The study comprised 30 patients with *complete transposition of the great vessels* admitted to The Hospital for Sick Children, Toronto, Canada. The diagnosis was confirmed by cardiac catheterization, angiocardiography, and surgery in all and by autopsy in 6. The ages of the patients ranged from 3 days to 12 years.

Serial preoperative and postoperative standard 13 lead electrocardiograms were obtained on each patient using the Sanborn direct writer electrocardiograph. The diagnostic criteria used for atrial and ventricular hypertrophy are those of Keith and associates.[9]

Preoperative and postoperative vectorcardiograms were recorded with the Frank lead system in 5 patients using the DR 8 Electronic for Medicine recorder. The findings will be presented briefly in illustrative examples. The patients were divided into two major groups.

*Group I* included 28 patients in whom an atrial septal defect was surgically created during the first month of life or later. The age at the time of operation is shown in Table I. This group was further divided into two subgroups according to the presence or absence of ventricular septal defect. *Subgroup Ia* included 16 patients with an intact ventricular septum. *Subgroup Ib* included 12 patients with a

From the Department of Cardiology and the Research Institute, The Hospital for Sick Children, Toronto, and the Department of Paediatrics, University of Toronto, Toronto, Canada.
This work was supported by grants from the Ontario Heart Foundation.
Received for publication Nov. 15, 196[illegible].
*Present address: The Children's Hospital, 19th Ave. and Downing, Denver, Colo. 80218.

ventricular septal defect, one of whom had pulmonary stenosis.

*Group II* included 11 patients in whom complete repair was effected by the Mustard operation. Nine patients had an intact ventricular septum, 7 of these were from Subgroup 1a. One patient had undergone a Blalock-Taussig anastomotic procedure and one had a large atrial septal defect. Two patients were from Subgroup 1b.

*Table I. Age at time of creation of an atrial septal defect*

| Age | Number of patients |
|---|---|
| 1 wk | 2 |
| 2 wk | 7 |
| 1 mo | 3 |
| 2 mo | 6 |
| 4 mo | 3 |
| 6 mo-1 yr | 4 |
| 1½ yr | 1 |
| 3 yr | 1 |
| 4 yr | 1 |

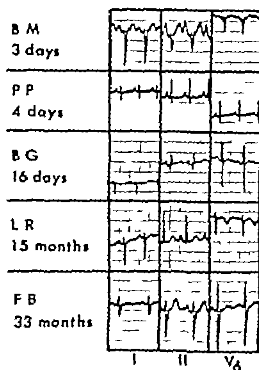



Fig. 1. Preoperative morphology of T wave in Leads I, II, and V₆ in 5 patients with complete transposition of the great vessels. It varied from normal configuration in Patient B M to flattening in Patients P P and B G, inversion in Patient L R, and dome-shaped with notching in Patient F B.

### Results

*Group I. Effect of surgical creation of atrial septal defect on the electrocardiogram*

PREOPERATIVE FINDINGS

Rhythm. Sinus rhythm was present in all patients. The P-R interval was within normal range in all; the average was 0.12 sec.

P Wave. Right atrial hypertrophy was evident in 16 patients (56.6 per cent) as indicated by a peaked P wave with an amplitude of 2.5 mm. or more. In the remainder of the patients the P wave was somewhat peaked, but the amplitude was normal. The range of P-wave duration varied between 0.04 and 0.08 sec., with an average of 0.05 sec.

Mean QRS Axis in Frontal Plane. The mean QRS axis showed a wide scatter in the frontal plane. In 20 patients it was directed to the right and inferiorly (right axis deviation, range +90 to ±180 degrees). In 3 patients it was oriented to

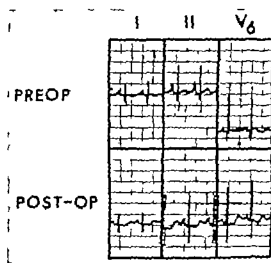



Fig. 2. Preoperative and postoperative electrocardiograms (Leads I, II, and V₆) of Patient B G. The preoperative tracing showed a flat T wave, peaked P wave 5 mm. in amplitude, and deep Q wave. In the immediate postoperative tracing the P and Q wave diminished in amplitude and the T wave increased in magnitude.

the left and inferiorly (50 degrees in 1 and 80 degrees in 2) and to the right and superiorly in 5 patients (−170 degrees in 3 and −120 and −110 degrees in the other 2)

Morphology of QRS Complex in Lead $V_1$ In Subgroup 1a an Rs pattern was found in 13 patients a qRs in 2 and an isolated tall R in 1 patient In subgroup 1b an RS pattern was noticed in 6 patients (50 per cent) an Rs in 2 a tall R in 2 and an rS pattern in 1 patient

Ventricular Hypertrophy In Subgroup 1a a pattern of right ventricular hypertrophy was present in 15 patients In 1 patient combined ventricular hypertrophy was manifested by a Q wave in Lead $V_6$ over 2 mm in amplitude In Subgroup 1b combined ventricular hypertrophy was present in 5 patients and right ventricular hypertrophy in 7

T Wave The morphology of the T wave in standard Lead I and left precordial leads was variable (Fig 1) It was either flat notched dome shaped or inverted The amplitude was markedly small in all cases in Subgroup 1a but in Subgroup 1b it was higher The frontal T

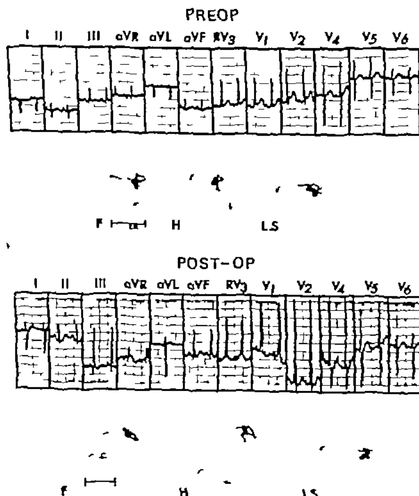



Fig 3 The electrocardiogram and vectorcardiogram before and after creation of an atrial septal defect in a 6-month-old infant Note the changes in both the P and T vectors In the postoperative electrocardiogram the P wave has become notched in Lead II and diphasic in Lead RV and V The increase in the magnitude of the T vector is more apparent in the vectorcardiogram

vector was directed inferiorly either left ward or rightward (range of 30 to 120 degrees) The horizontal T vector was oriented anteriorly producing an upright T wave in right precordial leads

POSTOPERATIVE FINDINGS The rhythm was nodal in 2 patients and normal sinus in the others

The P wave became notched and its amplitude diminished in 26 of the 28 patients Its duration was prolonged to an average of 0 085 sec an increase of 0 035 sec from the preoperative value (Fig 2) In the right precordial leads the P wave became diphasic after being upright (Fig 3) A pattern of combined atrial hypertrophy developed in 12 patients and left atrial hypertrophy in 11 and there was no change in 5 patients

No change was noted in the direction of the mean QRS axis in the frontal plane or the duration of QRS complex

In the right precordial leads an rR or rsR pattern was noted in 90 per cent of the cases

Three patients in Subgroup 1a developed combined ventricular hypertrophy after an atrial septal defect had been created In 2 patients a deep Q wave in Leads I and V6 diminished in amplitude in the immediate postoperative period (Fig 2)

T Wave The T wave increased in amplitude in 75 per cent of the cases It became taller and assumed a normal configuration This change was more noticeable in Subgroup 1a (Fig 3) In the horizontal plane the T vector tended to rotate leftward and posteriorly producing a negative T wave in the right precordial leads Serial examination of the electrocardiogram with increasing age in 4 patients showed that the T wave reverted back to its preoperative shape being either flat or inverted

*Group II Effect of total correction (Mustard operation) on the electrocardiogram* Arrhythmia was commonly noted in the immediate postoperative period (Fig 4) Nodal rhythm was observed in 5 patients Atrial flutter developed in 5 patients but responded quickly to digitalis therapy One patient had nodal tachycardia with intraventricular conduction defect (Fig 4)

The P wave diminished in amplitude and its configuration was altered It appeared

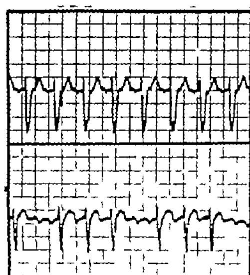


Fig 4 Standard Lead II Postoperative arrhythmia in 2 patients after total correction The upper tracing (R N 12 years old) is an example of atrial flutter with 2 1 block or it could be a nodal tachycardia with retrograde 2 1 block Note the inverted notches on the upstroke of the T wave which step out exactly with the obvious inverted P waves The lower tracing (B G 2 years old) is an example of atrial flutter

flat in 9 patients (Fig 5) and in 2 patients it was dome shaped The P R interval was prolonged in 3 patients (0 18 sec in 2 and 0 20 sec in 1) but was within normal limits in the other patients

The T wave increased in magnitude and was upright in 8 patients diphasic in 2 (Fig 5B) and inverted in 1 after being upright In 2 patients the electrocardiogram 18 months postoperatively showed the T wave to be diphasic in Leads I and V6 after being upright

**Discussion**

The electrocardiographic picture in complete transposition of the great vessels is variable depending on the underlying pathophysiology[4,6] Right ventricular hypertrophy is the usual pattern in cases with intact ventricular septum and low pulmonary vascular resistance whereas combined ventricular hypertrophy is common in the presence of ventricular septal defect and elevated pulmonary vascular resistance

The resultant physiologic effect after surgical creation of atrial septal defect as

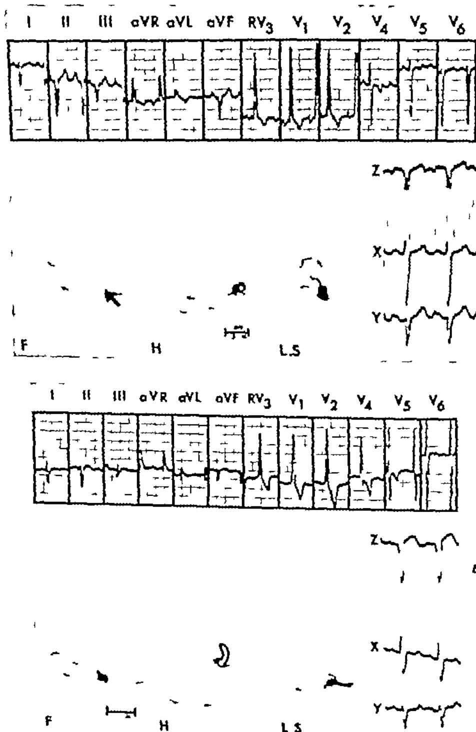



Fig. 5A The preoperative electrocardiogram and vectorcardiogram of a 12 year-old boy with complete transposition of the great vessels who underwent a Blalock-Taussig anastomotic procedure during [illegible] The loops are suggestive of combined atrial and right ventricular hypertrophy.

Fig. 5B The electrocardiogram and vectorcardiogram of the same patient as in Fig. 5A after total repair with the Mustard operation. Notice the flattening of the P wave in the standard and orthogonal leads. The R wave in Leads V[illegible] and V[illegible] returned to a relatively normal amplitude. In the horizontal plane the inscription of the QRS loop is clockwise and the loop is displaced more to the left than preoperatively.

demonstrated by Shaher and Kidd[19] are an increase in the degree of bidirectional shunting at the atrial level, improvement in the systemic arterial saturation, increase in the systemic blood flow, and a diminution in the calculated pulmonary blood flow.

Electrically, this was manifested by changes in cardiac depolarization and repolarization.

In the preoperative electrocardiogram, right atrial hypertrophy was noted in 56.6 per cent, whereas postoperative notching, prolonged duration, and diminished amplitude of the P wave were observed in 90 per cent. These P wave changes suggestive of combined or left atrial enlargement could represent an actual increase in atrial work secondary to a step-up in bidirectional shunting. Against this hypothesis is the fact that the left atrial pressure in 60 per cent of the group of patients studied by Shaher and associates remained essentially unchanged after creation of the atrial septal defect. Moreover, the diminution in the calculated pulmonary blood flow exceeded the increase in the bidirectional shunt at the atrial level. Alternatively, these P wave changes could have been due to the traumatic effect of surgical excision of the atrial septum.

Several authors[6,8,10] described the T wave changes noted in this study in Standard Lead I and the left precordial lead. It was suggested that the flat and inverted T wave could be due either to excessive pulmonary blood flow with overloading of the left ventricle or to myocardial ischemia. After the creation of an atrial septal defect the T wave increased in magnitude and became upright in the majority of patients. Such changes are most likely due to the rise in systemic arterial saturation with better oxygenated perfusion of the myocardium.

The appearance of an rR or rsR pattern in the right precordial leads of the postoperative electrocardiogram in Group I is of significance since it indicates volume overloading of the right ventricle secondary to the increase in systemic blood flow. Diminution in the calculated pulmonary blood flow was suggested by the decrease in the magnitude of the Q loop in Leads I and $V_6$.

The Mustard operation in patients with complete transposition of the great vessels involves excision of the atrial septum and the insertion of a pericardial baffle in such a way as to divert the pulmonary venous return into the right ventricle and the systemic venous blood flow into the left ventricle. The prolonged P-R interval and flattening of the P wave seen in the electrocardiogram after total repair is due to surgical trauma.

No marked changes were observed in ventricular hypertrophy patterns after total correction. One expects a change only if complications occur, such as pulmonary venous obstruction or progression of pulmonary vascular disease.

Arrhythmias were commonly observed in the immediate postoperative period, but these were transitory and responded to medical therapy.

## Summary

The electrocardiograms of 30 patients with complete transposition of the great vessels were analyzed before and after surgical creation of an atrial septal defect and after total repair with the Mustard procedure. The effect of surgery was manifest in changes in the P and T waves and to a lesser extent in the ventricular hypertrophy pattern. Arrhythmia was commonly noted in the immediate postoperative period.

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# Experimental and laboratory reports

## Valvular heart disease in the monkey (*Macaca mulatta*)

*William C. Roberts, M.D.**
*J. R. M. Innes, Sc.D. (Cantab.), M.R.C.V.S., F.C.Path.*
*Bethesda, Md.*

In contrast to the very high incidence in man, cardiac diseases in animals constitute a small percentage of their total diseases. Despite their infrequency, however, cardiac diseases occur in almost all animal species. Most reports of spontaneous cardiac disease in animals have concerned dogs, cats, and horses, probably because these species are most frequently observed and their life spans are relatively long.

Among the cardiovascular diseases found in monkeys, systemic hypertension appears to be the most frequent and arteriosclerosis among the least common.[1] Myocardial infarction is extremely rare in monkeys, although electrocardiographic evidence of coronary arterial insufficiency is occasionally present and small focal myocardial scars are occasionally seen at necropsy. Acute and chronic endocarditis has been reported rarely in monkeys.[1-4] Scott[5] in 1927 and Hamerton[6,7] in 1939 each described a simian case of polypoid ulcerative endocarditis with systemic emboli. Several years later, Hamerton[8,9] described sclerosis of the cardiac valves of 2 old baboons, but few details were given. Lapin and Yakovleva[1] described 2 monkeys which had mitral stenosis and regurgitation and diffusely scarred, contracted, and fused mitral leaflets and chordae tendineae. The etiology of the mitral disease in these monkeys was not determined, but the authors believed that infective endocarditis which had healed was the most likely explanation. In addition, these investigators described 4 other monkeys which had acute endocarditis of the mitral valve, and in 1 a large polypoid vegetation was present.

Among over 1,000 simians necropsied during the past 18 months at the Bionetics Research Laboratories,† 2 were found to have valvular cardiac disease. One of these monkeys had a scarred mitral valve which was both stenotic and incompetent, and the second had acute endocarditis of both mitral and aortic valves leading to aortic stenosis. A description of the clinical and pathologic findings in these 2 monkeys forms the basis for this report.

### Clinical and necropsy observations

*Monkey 1 (65-566).* The monkey was an adult breeding female (exact age uncertain) which arrived pregnant, later aborted, and still later had a live baby. Available clinical data are meager. Fig. 1 is an elec-

From the Laboratory of Pathology, Clinic of Surgery, National Heart Institute, National Institutes of Health, Bethesda, Md., and the Bionetics Research Laboratories, Falls Church, Va.
This study was supported (J.R.M.I.) by Research Contract PH 43-63-412, National Cancer Institute, National Institutes of Health, United States Public Health Service.
Received for publication Nov. 3, 1965.
*Address: Chief, Laboratory of Pathology, Clinic of Surgery, National Heart Institute, National Institutes of Health, Bethesda, Md. 20014.
†These monkeys included mature males and females, mostly [illegible] in Africa.

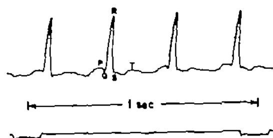



Fig 1 Monkey 1 Lead II of the electrocardiogram recorded approximately 12 hours before death in a monkey with mitral valvular disease




Fig 2 Monkey 1 Exterior of the heart The left atrial appendage (*L A A* ) is severely dilated and totally obscures the pulmonary trunk Both the right (*R V* ) and left (*L V* ) ventricles are enlarged as is the right atrial appendage (*R A A* ) The right middle lobe (*R M L* ) of the lung is collapsed and histologic sections disclosed a hemorrhagic infarct *T* Trachea *A* Ascending aorta







Fig 3 Monkey 1 Left atrium *Top* The left atrium (*L A* ) extremely dilated thin walled and free of clot Just above the mitral valve the endocardium is focally thickened probably secondary to a jet lesion of mitral regurgitation The leaflets of the mitral valve are thickened particularly the margin and the chordae tendineae are short and thick A small perforation in the posterior half of the anterior mitral leaflet is indicated by the arrow *Center* Close-up view of the opened mitral valve The cut transects the posterior (*P*) leaflet *A* Anterior leaflet *Bottom* The mitral valve as seen from the left atrium before it was opened The orifice of the valve is more or less fixed and its size probably changed little during the cardiac cycle The valve is both stenotic and incompetent

trocardiogram recorded about 12 hours before death when the monkey was in a state of severe congestive cardiac failure with ascites and tachycardia (220 beats per minute) Despite massive left atrial dilatation sinus rhythm was present Shortly after the electrocardiogram was made the monkey was given digoxin and several hours later the heart rate was approximately 125 beats per minute The animal died shortly thereafter

At necropsy large quantities of fluid were present in the pleural and peritoneal cavities and the liver was firm and nodu




Fi 4 M ke 1 Op l left atrium (LA) [illegible] Both anterior (AL) [illegible] posterior (PL) mitral leaflet and [illegible] tendineae [illegible] and shortened but free [illegible] from [illegible] The hypertrophy and dilatation of the left [illegible] further [illegible] mitral regurgitation [illegible] the [illegible] normal [illegible] left atrium

lar. The kidneys were normal. Cultures of the heart blood and mitral valve grew only contaminants.

The heart was markedly enlarged (Fig. 2). The mitral valve was contracted, fibrotic, and both stenotic and incompetent (Figs. 3-5). A small smooth-walled perforation, which probably was of little hemodynamic significance, was present in the anterior mitral leaflet. All cardiac chambers were dilated, the left atrium to aneurysmal proportions, and both ventricles were hypertrophied. The aortic and pulmonic valves were normal, as were the tricuspid valvular leaflets and chordae tendineae, but the tricuspid annulus was dilated (Fig. 6). The marked dilatation of the right atrium suggested that the tricuspid valve, although anatomically normal, was functionally incompetent. Additional evidence is provided by the severe centrolobular hepatic congestion and necrosis (Fig. 6).

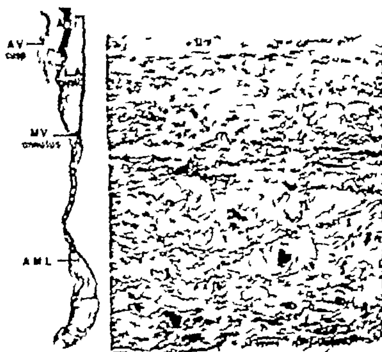



Fig. 5. Monkey 1. Photomicrographs of mitral valve and left atrium. *Left*: The section includes the anterior mitral leaflet (AML), mitral valve (MV) annulus, left atrial (LA) wall, an aortic valve (AV) cusp and ascending aorta (Ao). The thickening of the mitral valve is due entirely to proliferation of fibrous tissue. [illegible] channels are present in the thickened mitral leaflet. *Right*: Section of left atrial wall shows severe hypertrophy and degeneration of myocardial fibers. No Aschoff bodies or inflammatory cells were seen in any section of the heart. Elastic tissue stain, × [illegible] (*left*); hematoxylin and eosin, ×135 (*right*).




Fig. 6 Monkey 1. Right side of the heart and liver. *Left*: Opened right atrium (*R.A.*), inferior vena cava (*I.V.C.*, *dashed line*), tricuspid valve and right ventricle (*R.V.*). The right atrium, coronary sinus ostium (*C.S.*) and tricuspid valve ring are markedly dilated, apparently the result of relative tricuspid regurgitation, which in turn was secondary to the presumed pulmonary hypertension. *Right*: Photomicrograph of liver showing severe centrolobular congestion and necrosis. This type of hepatic change is characteristically seen in severe right-sided cardiac failure. Hematoxylin and eosin ×65.

Histologic sections showed only fibrous thickening of the mitral valvular leaflets. No Aschoff bodies were seen in any of the multiple sections of the heart. The myocardial fibers of all cardiac chambers were hypertrophied and in addition many of those in the left atrium were degenerated. Inflammatory cells were not present in the myocardium or mitral valve. The pulmonary veins and alveolar capillaries were distended and congested. Neither the pulmonary arteries nor veins had thick walls.

*Monkey 2 (65 1635)*. The animal belonged to an untreated control group of *Macaca mulatta* and had been under observation at Bionetics Research Laboratories for 6 months. A tuberculin skin test performed when the animal arrived was negative. The animal had diarrhea periodically but multiple bacteriologic and parasitologic examinations of the feces were unremarkable.

The cardiac changes observed at necropsy are described in detail in Figs. 7–13. In summary, there was diffuse adhesive fibrous and fibrinous pericarditis, diffuse inflammatory thickening of the aortic valvular cusps causing aortic stenosis, similar inflammatory thickening of the anterior mitral leaflet but probably no mitral stenosis or incompetence, myocarditis with focal abscess formation and vasculitis, and severe left ventricular hypertrophy. Sections of the valvular cusps, pericardium and myocardium which were stained for pyogenic and tuberculous bacteria, fungi and spirochetes were negative. No Aschoff bodies were seen in the sections of heart. In addition to the cardiac findings there was diffuse acute pulmonary edema but no hydrothorax or ascites. Multiple disseminated lesions of pulmonary ascariasis also were present.

## Comments

The etiology of the valvular heart disease in each of these monkeys is speculative. Neither organisms nor Aschoff bodies were found in histologic sections of the hearts in either animal. Indeed, rheumatic disease of the heart with Aschoff bodies has never been reported in domestic animals. In some respects the appearance of the mitral

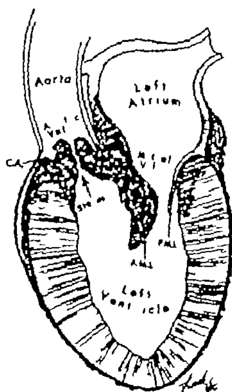



Fig. 7. Monkey 2. Diagram of heart. The aortic valvular cusps and the anterior mitral leaflet (A.M.L.) are markedly thickened and the aortic valve is stenotic. The posterior mitral leaflet (P.M.L.) is normal. The inflammatory process (dark shading) also involved the atrial wall, left ventricular wall, and pericardium. The inflammation bulging beneath the proximal portion of the left coronary artery (C.A.) causes narrowing of this vessel.

valve in Monkey 1 resembles rheumatic mitral disease in human beings in that the scarring process was diffuse, involved both leaflets as well as all chordae tendineae, and was most pronounced at the margins of the leaflets. The presence of vascular channels in the scarred mitral leaflets in Monkey 1 is no indication of a rheumatic etiology, since in human beings vessels may be seen in mitral valves altered by congenital malformations, trauma, and in Marfan's syndrome, as well as by rheumatic fever, and vessels are present normally in cardiac valves in some monkeys.[1] Severe degeneration of the myocardial fibers of the atria in this animal is more in favor of a rheumatic process, since this disease always involves the left atrial wall,[14] but it is possible that chronic left atrial dilatation from any cause would produce a similar change. The perforation in the anterior mitral leaflet in this monkey also is difficult to explain on the basis of rheumatic disease. An infection which subsequently healed appears to be the most reasonable explanation of the perforation and possibly also of the diffuse scarring of the leaflets.

The etiology of the pericarditis in Monkey 2 is purely speculative. The anatomic appearance of the valvular lesions in this animal seems to be unique, and we are not




Fig. 8. Monkey 2. Opened heart. Left. The left ventricle (L.V.), aortic valve (A.V.), and aorta are opened. Each of the three aortic cusps are thick, as is the anterior mitral leaflet (A.M.L.). The focal area of acute inflammation (Abscess) beneath the left coronary artery (L.C.A.) is indicated. P.T., Pulmonary trunk. Right. The opened left atrium (L.A.), mitral valve, and left ventricle are shown. The anterior leaflet (A.M.L.) is diffusely thickened, and the posterior mitral leaflet (P.M.L.) is normal.




Fig. 9 Monkey 2. Exterior of heart (*left*) and transverse section of ventricles (*right*). The visceral pericardium is shaggy. The left ventricular wall (*L.V.*) is markedly hypertrophied. *R.V.* Right ventricle. *R.A.A.* Right atrial appendage. *L.A.A.* Left atrial appendage. *Ao.* Ascending aorta. *P.T.* Pulmonary trunk. *V.S.* Ventricular septum.

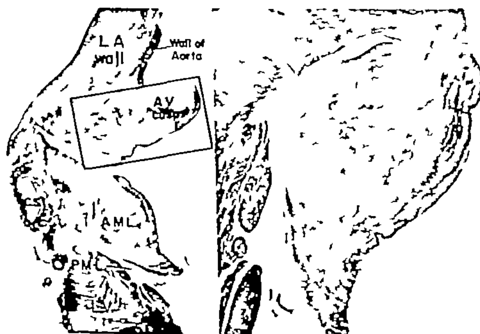



Fig. 10 Monkey 2. Photomicrographs of the aortic and mitral valves. *Left.* Section includes a thickened aortic valvular cusp (*A.V.*), the thickened anterior mitral leaflet (*A.M.L.*) and the normal posterior mitral leaflet (*P.M.L.*). The left atrial (*L.A.*) and left ventricular (*L.V.*) walls and coronary sinus (*C.S.*) are indicated. This section illustrates the continuity of the aortic valve, anterior mitral leaflet and left atrial wall. The inflammatory process involved all of these structures. A close-up of the area within the rectangle constitutes Fig. 11. *Right.* A close up of the anterior and posterior mitral leaflets. Hematoxylin and eosin stains. ×4.5 (*left*), ×12 (*right*).



Fig 11 Monkey 2 The aortic valve cusp and its ring from the area within the rectangle in Fig 10 A band of necrotic debris is present in the cusp in addition to numerous inflammatory cells Several fresh abscesses are present in the ring A close up of the small area within the rectangle constitutes Fig 12 Hematoxylin and eosin stain ×19



Fig 12 Monkey 2 Area of aortic valvular cusp marked by rectangle in Fig 11 Collections of acute inflammatory cells and necrotic debris are present Hematoxylin and eosin stain ×260

aware of a previous report describing a necrotizing inflammatory process of similar distribution in either man or monkey. Each of the cusps of the aortic valve in this monkey were diffusely and uniformly thickened by the inflammatory process but only the anterior leaflet of the mitral valve was involved the posterior one being entirely normal. Since the anterior mitral leaflet is continuous with the aortic valvular cusps it would appear to be reasonable to assume that the necrotizing inflammatory process extended directly from one valve to the other. Whether this process began in the endocardium of these cardiac valves on the left side and subsequently spread by direct extension to the adjacent myocardium and finally to the subepicardial adipose tissue and pericardial surfaces or whether the process initially began in the pericardium and spread inward is not known. That the endocardial surfaces of the involved aortic and mitral leaflets are smooth is some evidence that the process did not begin as a vegetation but as a process within the valve leaflets



Fig 13 Monkey 2 Acute pericarditis and myocarditis *Left* Section of subepicardial blood vessel which acutely inflamed *Right* Section of left ventricle demonstrating focus of acute inflammation Hematoxylin and eosin stains ×175 (*left*) ×260 (*right*)

At autopsy there was no evidence of mediastinitis Frank areas of fibrinoid necrosis were present within the aortic and mitral leaflets and the rings of each of these valves contained abscesses Similar acute inflammatory cell were present within the valve leaflets myocardium and pericardium Although the predominant cell appeared to be the polymorphonuclear leukocyte the inflammatory process must have been present for some time as evidenced by the severe left ventricular hypertrophy

## Summary

Valvular heart disease of unknown etiology is described in each of 2 monkeys One had chronic scarring of the mitral valve which was both stenotic and incompetent and the second had acute necrotizing inflammation of the aortic valve which was stenotic and of one cusp of the mitral valve

The photomicrographs were taken by M Gebhard Gsell

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# The temporal sequence of lymph flow in the right lymphatic duct in experimental chronic pulmonary edema

*H N Uhley M D**
*S E Leeds M D*
*J J Sampson M D*
*N Rudo M D*
*M Friedman M D*
*San Francisco Calif*

In 1942 Warren and Drinker[1] measured pulmonary lymph flow in dogs with acute pulmonary edema produced by compression of the pulmonary veins and observed that lymph flow increased Studies by Rabin and Meyer[2] and in our laboratory[3,4] confirmed that pulmonary lymph flow increased with elevation of left atrial pressure however these increases were insufficient to prevent the development of overt pulmonary edema We subsequently devised a technique for the development of chronic heart failure in dogs[5] and demonstrated that in chronic failure the right lymphatic duct channels which drain nearly all of the canine lung[6] expand and gross increases in pulmonary lymph flow occurred The current study attempts to determine the time sequence involved in the expansion of the pulmonary lymphatic channels and the concomitant rise in pulmonary lymph flow in the development of heart failure

## Methods

Eighteen mongrel dogs weighing between 12 and 20 kilograms were used in this study They were anesthetized with intravenous sodium pentobarbital (29 mg per kilogram) and a side to side 7 to 10 mm aorticocaval anastomosis was made below the renal vessels by approximating and suturing the aorta and vena cavae The animals were given 25 mg of desoxy corticosterone trimethylacetate† twice a week and were placed on a salt enriched diet of approximately 6 Gm of salt per day

In the first group of 8 animals lymph from the right lymphatic duct was collected immediately prior to and 1 day after the A V fistula operation In another group of 5 dogs the lymph flow was observed 10 days after the operation In a third group of 5 dogs lymph flow was observed 20 days after the operation and a single animal was studied 28 days after the operation

With the technical assistance of [illegible] B S and [illegible] R N
From the Department of Experimental Surgery and Pathology and the Harold Brunn Institute [illegible] Zion Hospital and Medical Center San Francisco Calif
Supported by Grant HE-03180-09 from the National Heart Institute National Institutes of Health U S Public Health Service
Received for publication Nov 10 1965
*Address Mount Zion Hospital and Medical Center 1600 Divisadero St San Francisco Calif 94115
†Percorten Ciba

On the day on which the animals were studied they were anesthetized with intravenous pentobarbital (29 mg per kilogram) placed on an intermittent positive pressure respirator and given 3 to 5 c c of 2 per cent Evans blue dye intratracheally Lymph from the lungs was collected by an improved technique recently developed in this laboratory[7] which permitted continued collection on the following day in the unanesthetized dog if so desired The right external jugular vein was exposed and a segment of that portion which contained the entrance of the right lymphatic channels was isolated with umbilical tape ligatures Venous tributaries leading into the segment were also ligated The cephalad end of the isolated vein was cut and fitted over a small polyethylene cannula After the residual blood was aspirated the incision in the skin was closed and lymph flowing into the venous segment was collected In this manner it was possible to use the external jugular vein as a fistula for the serial collection of lymph from the right lymphatic duct

In the first group of 8 dogs the method was utilized to collect lymph from the unanesthetized animal 1 day postoperatively but in the remaining group the dogs were anesthetized lymph flows were obtained and after thoracotomy left atrial pressures were recorded by inserting a tube attached to a manometer into the left atrial appendage After pressure was measured lung biopsies were obtained and the respirator was stopped Necropsy was performed immediately and pulmonary edema was estimated by the gross appearance of the lungs and the ratio of lung weight to body weight[8] Cardiomegaly was estimated by the ratio of heart weight to body weight[9]

## Results

The mean preoperative flow was 5 ml per hour (4 6 2) and 1 day postoperatively the mean flow was 9 ml per hour (4 9 13) (Fig 1) These animals did not demonstrate any signs of acute heart failure

In the group of animals studied 10 days postoperatively edema of the hind limb

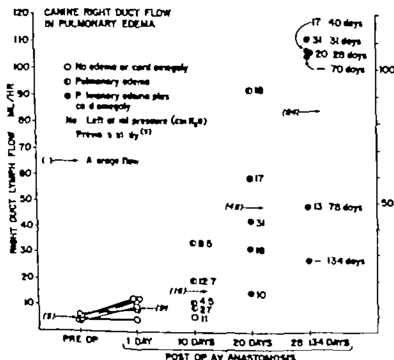



Fig 1 The temporal sequence of lymph flow in the canine right lymphatic duct in experimental chronic pulmonary edema Note the increased increments in mean flow in the right lymphatic duct after the tenth day

# Electrocardiographic cancellation

## A study of a single dipole at variable locations

*Robert A. Helm, M.D.*
*Te Chuan Chou, M.D.*
*Cincinnati, Ohio*

Electrocardiographic cancellation provides a technique which has been used rather extensively to investigate the validity of representing the heart as a single dipole variable in strength and axial orientation but constant in location.[1-9] The conclusions drawn from such studies have been conflicting. It is the purpose of this paper to clarify the significance of electrocardiographic cancellation by reporting computations of cancellation patterns obtained when the location of a single dipole varies in a well defined manner with each change in dipole strength and axial orientation. These computations were carried out by means of previously described mathematical techniques.[10]

### Methods

Fig. 1 represents the basic model utilized in this study and will hereafter be designated as Model I. The location of the dipole is postulated to move through a distance of 1 cm. at 4 msec. intervals. The locations of the dipole at each of these time intervals are arbitrarily placed at one of the dipole points on the transverse plane of Frank's model[11] and these are depicted and labeled in Fig. 1. The arbitrarily chosen magnitudes of the X and Z components of the dipole at each location are also given in ma. cm. in Fig. 1. All of the dipole orientations are such that there are no Y components.

Fig. 2 represents a modification of the basic model in which all of the consecutive dipole locations, as well as the orientation of the dipole at each location, have been rotated counterclockwise through 90 degrees. Comparison of Figs. 1 and 2 will clarify the differences between these models. The model depicted in Fig. 2 will hereafter be designated as Model II.

The x and z components of the image vectors for each of the dipole locations are those published by Frank (see appendix of Reference 11). The polarities of Frank's z components are reversed, however, in order that lead polarity might be identical with that of conventional precordial leads. Frank's data were normalized and converted to mv./ma. cm. in accordance with the methods described in the appendix of Reference 11.

Figs. 3 and 4 represent the scalar patterns obtained with various leads with Models I and II, respectively. In the inserts of Figs. 3 and 4 are diagrams of Frank's transverse plane showing the location of the 6 cm. square along the periphery of which the dipole migrates 1 cm. every 4

From the Cardiac Laboratory, Cincinnati General Hospital, and the Department of Medicine, College of Medicine, University of Cincinnati, Cincinnati, Ohio.
Supported in part by the [illegible] Fund for Electrocardiographic Research, College of Medicine, University of Cincinnati, and in part by funds received from the Heart Association of Southwestern Ohio, Inc.
Received for publication Nov. 22, 1963.

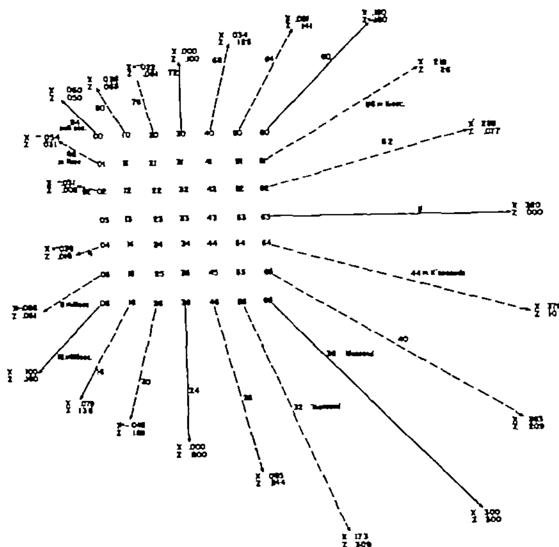


Fig. 1. The basic model referred to in the text as Model I depicts the magnitude of the X and Z components of the variably located dipole in ma-cm. The dipole moves through a distance of 1 cm at 4 msec intervals. The numbers constituting the 6-cm square refer to the dipole locations on the transverse plane of Frank model. The x and z components of the image vectors for each of the dipole location are listed in the appendix of Reference 11.

msec. Leads are formed by determining the differences in potential which would exist at each 4 msec interval between any of the 16 points A through P located on the boundary of the transverse section. Each such difference in potential represents the sum of the product of the X component of the dipole vector and the x component of the lead's image vector and the product of the Z component of the dipole vector and the z component of the lead's image vector.

As developed in the previous publication,[10] the general equation for an electrocardiographic cancellation may be written as

$$R = P - Q(q_1L_1 + q_2L_2 + q_3L_3 + \cdots + q_nL_n)$$

where R is the cancellation voltage, P is the voltage of the lead being cancelled, and the L terms represent the voltages of the leads which are summated to produce the cancellation. All of these voltages vary with time. The Q and q terms are coefficients

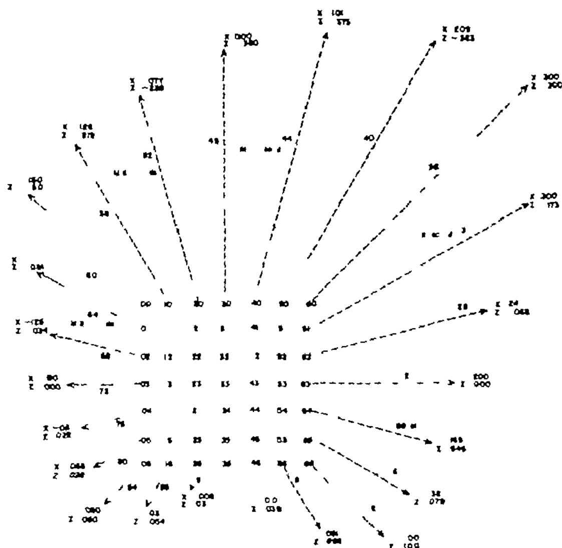


Fig. 2. The basic model illustrated in Fig. 1 has been modified and is referred to in the text as Model II. The consecutive dipole locations have been rotated counterclockwise through 90 degrees and the orientation of the dipole at each location has also been rotated counterclockwise through 90 degrees.

which remain constant throughout the entire cardiac cycle or any designated portion of it. Q may have any positive or negative value but $(q_1 + q_2 + q_3 + \ldots + q_n) = 1$ in all instances.

As an example of the application of this equation, the voltages of the four points C, G, K, and O depicted in the inserts of Figs. 3 and 4 may be considered. Let P = (C-K), $L_1$ = (O-K), and $L_2$ = (G-K), where the letter designations of the points in question are also used to represent their voltages. Then

$$R = (C-K) - Q[q_1(O-K) + q_2(G-K)] \qquad (1R)$$

representing what will be referred to in this paper as an R cancellation.

Considering again the voltages of the four points C, G, K, and O in conjunction with the general cancellation equation, let P = (C-O), $L_1$ = (C-K), and $L_2$ = (G-O). If, for convenience of notation, R is replaced by the small case letter r,

$$r = (C-O) - Q[q_1(C-K) + q_2(G-O)]$$

where Q, $q_1$, and $q_2$ are coefficients having different numerical values but the same significance as in Equation (1R). Let $Qq_1 = m$ and $Qq_2 = n$. With rearrangement

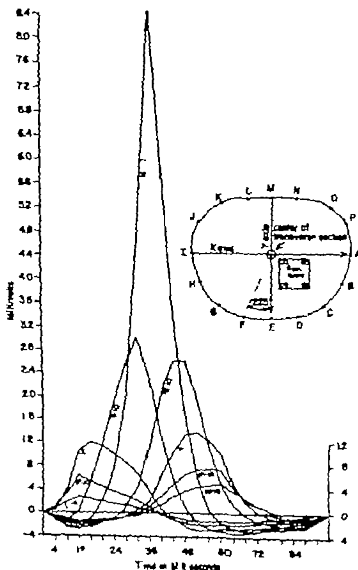



Fig 3 The insert depicts the position on the transverse plane of the 6-cm square about which the dipole migrates in Figs 1 and . The points through P on the periphery of the transverse plane indicate the location of electrodes The graphs represent the differences in potential between various electrode points calculated from the vectors of Model I (Fig 1) in conjunction with the mean vector data published by Frank

$$r = [(1 - m)C + mK] - [(1 - n)O + nG] \quad (1r)$$

representing what will be referred to in this paper as an r cancellation

The following four point R cancellations were explored in this study in addition to that expressed by Equation (1R)

$$R = (C - K) - Q[q(P - F) + q(F - K)] \quad (2R)$$
$$R = (C - K) - Q[q(A - K) + q(F - K)] \quad (3R)$$
$$R = (C - K) - Q[q(B - K) + q(D - K)] \quad (4R)$$

The following four point r cancellations were utilized in this investigation in addition to that expressed by Equation (1r)

$$r = [(1 - m)C + mK] - [(1 - \;)P + \;F] \quad (2r)$$
$$r = [(1 - m)C + mK] - [(1 - n)A + \;F] \quad (3r)$$
$$r = [(1 - m)C + mK] - [(1 - n)B + \;D] \quad (4r)$$

The following R cancellation involving more than 4 points on the surface of Frank's transverse plane was also studied

$$R = (C - K) - Q[q(O - K) + q(G - K) + q(H - N)] \quad (5R)$$

Another form of cancellation arbitrarily

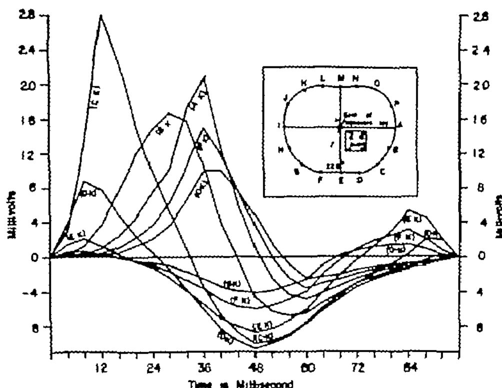



Fig. 4. This illustration corresponds to that of Fig. 3 except that the graphs are based on Model II rather than Model I.

designated as an R type may be derived as follows. Let $L_1$, $L_2$, and $L_3$ represent three separate leads which possess perfectly uniform, although not necessarily orthogonal, lead fields.[11] Substituting in the general equation for an electrocardiographic cancellation

$$R' = P - Q(q_1L_1 + q_2L_2 + q_3L_3)$$

where $Qq_1$, $Qq_2$, and $Qq_3$ become unique constants when the series of R' potentials is minimized by one of the techniques described in the previous publication.[19] The R' deflections then represent the minimal residual voltages resulting from the fact that the field of lead P is not uniform. Let $L_1 = (Xx_1 + Yy_1 + Zz_1)$, $L_2 = (Xx_2 + Yy_2 + Zz_2)$, and $L_3 = (Xx_3 + Yy_3 + Zz_3)$, where X, Y, and Z are the time varying components of the moving dipole and the nine lower case symbols are all separate constants as the result of the uniformity of the lead fields of $L_1$, $L_2$, and $L_3$. Then

$$R = P - (Xx + Yy + Zz) \qquad (R)$$

where x, y, and z must consequently also be unique constants when the series of R potentials is minimized. (The significance of the quantities x, y, and z and their relation to the components of the image vector of the fixed location of an equivalent dipole will be considered in the *Discussion*.) Since Models I and II of the present study do not possess Y components, the last equation is herein utilized in the following two dimensional form to assess the uniformity of the field of lead (C K)

$$R = (C\ K) - (Xx + Zz) \qquad (IR)$$

The foregoing equations are listed in this section to permit their recognition in the following sections by means of their marginal parenthetical designations. The symbols R, r, and R' can be furthermore defined by the subscripts r and s depending upon whether the residual voltages are calculated as a minimum range cancellation or a minimum root mean square cancellation, respectively. (Reference to the previous publication[19] will clarify the differences between these two types of cancellation patterns.)

Various cancellation coefficients can be used for the evaluation of an R cancellation Taking the four points C G K and O for illustrative purposes the following cancellation coefficients, $C_1$ $C_2$ and $C_3$ expressed in percent can be defined

$$C_1 = \frac{100\,R}{(C\,K)}$$

$$C_2 = \frac{200\,R}{(C\,K) + Q[q_1(O\,K) + q_2(G\text{-}K)]}$$

$$C_3 = \frac{100\,R^2}{(C\,K)^2}$$

$C_1$ is the coefficient advocated by one of the authors [10] $C_2$ has been used by Okada Langner and Briller [8] $C_3$ was utilized in another form by Scher Young and Meridith [9] for root mean square cancellation involving factor analysis [*] These coefficients can be adapted for the evaluation of R cancellations by substituting R for R in the numerators of the equations for $C_1$ $C_2$ and $C_3$ and in addition by substituting (\x + 2z) of Equation (1R') for $Q[q_1(O\,K) + q\ (G\,K)]$ in the denominator of the expression for C

For the evaluation of an r cancellation other coefficients $c_4$ $c_5$ $c_6$ and $c_7$ expressed in per cent can be defined

$$c_4 = \frac{400}{(C\,K) + (O\,G)}$$

$$c_5 = \frac{100r}{(1-m)[C-(1-n)O-nG] + m[K-(1-n)O-nG]}$$

$$c_6 = \frac{50r}{m[K-(1-n)O-nG]}$$

$$c_7 = \frac{50r}{C-(1-n)O-nG} + \frac{50r}{K-(1-n)O-nG}$$

Frank[4] applied the cancellation coefficient $c_4$ to his studies Schmitt and his associates[3] utilized $c_5$ as did Seiden and Kessman[4] and Brody and his co workers used $C_3$ in one publication[6] and $c_7$ in another[7]

All of the foregoing cancellation coefficients may be applied to either a minimum range or a minimum root mean square pattern [10] In the case of the latter the root mean square of the cancellation pattern (R R' or r) and the root mean squares of the expressions appearing in the denominator are substituted In the case of a minimum range pattern the minimum spread of the cancellation (R R or r) and the maximum spreads of the expressions appearing in the denominator are substituted

**Results**

The results of these studies are depicted graphically in Figs 5 through 11 In each illustration the graphs are numbered and the method of computing each may be determined from the correspondingly numbered equation listed in the illustration The values of x' and z of Q $q_1$ and q or of m and n may be determined by comparing the numerical values of the appropriate equation in an illustration with the symbols of the corresponding equation listed in the section entitled *Methods*

Minimum root mean square cancellations were computed for Models I and II and the results are shown in Figs 5 and 6 respectively In each of the latter illustrations Graph 1 was obtained by the application of Equation (1R ) and represents the residual voltages resulting from the lack of uniformity of the lead field of (C K) Graphs 2 3 4 and of Figs 5 and 6 obtained respectively by the application of Equations (4R) (3R) (2R) and (1R) illustrate the residual voltages when lead (C K) is cancelled by a combination of leads (B K) and (D K) a combination of leads (A K) and (E K) a combination of leads (P K) and (F K) and a combination of leads (O K) and (G K) respectively The graphs of these R cancellations demonstrate that as the anatomic axes of the two combined leads diverge from the anatomic axis of lead (C K) as depicted in the inserts of Figs 3 and 4 the cancellation voltages increase and the cancellation coefficients $C_1$ $C_2$ and $C_3$ likewise rise These increases in cancellation voltages tend to plateau and $C_1$ and $C_2$ approach 100 per cent whereas $C_3$ exceeds 100 per cent

Figs 7 and 8 illustrate minimum root mean square cancellations of the r type computed for the models shown in Figs

1 [illegible] published paper [illegible] [illegible] expressed [illegible] form which [illegible] (100-C ) The value of $C_3$ without [illegible] subtracted [illegible] [illegible] method of evaluating a cancellation to be compared more readily with $C_1$ and $C_2$ It should be noted that $C_3 = C_1$ 100.

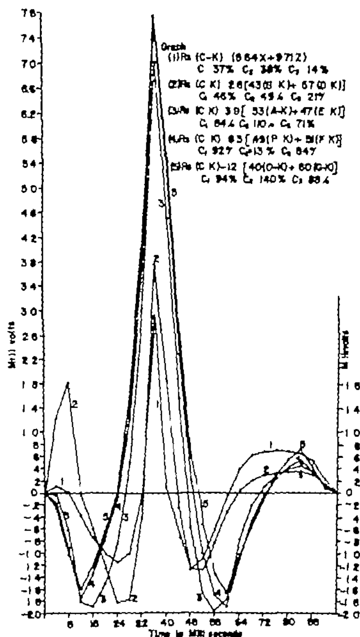



Fig. 9. The minimum root mean square cancellations were calculated for Model I. Graph 1 represents the residual voltages resulting from the lack of uniformity of the field of lead (C K). Graphs 2, 3, 4 and 5 illustrate the residual voltages when lead (C K) is cancelled by combinations of leads (B K) and (D K), of leads (A K) and (E K), of leads (P K) and (F K), and of leads (O K) and (G K), respectively.

1 and 2, respectively. It is apparent from inspection that these graphs represent residual voltages which are considerably smaller than the voltages of the R cancellations depicted by the graphs of Figs. 5 and 6. It is of interest that the magnitudes of the voltages of the cancellations illustrated in Figs. 7 and 8 decrease as the electrodes adjacent to point C are moved to locations more distant from this point. Despite this diminution, the corresponding cancellation coefficients $c_?$, $c_?$, and $c_?$ increase or remain approximately constant. However, the cancellation coefficient $c_?$ decreases in the same manner as the cancellation voltages diminish when the electrodes

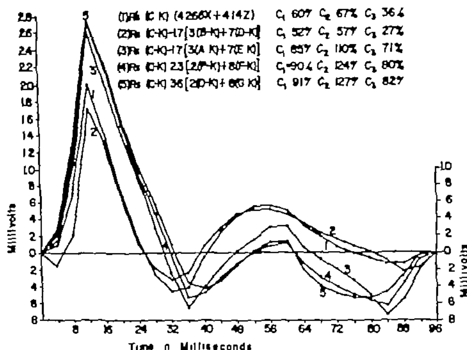



Fig 6 The illustration corresponds to that of Fig 5 except that the graphs are based on Model II rather than Model I

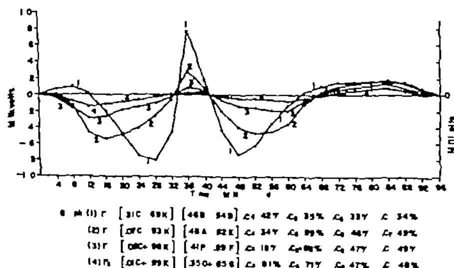



Fig 7 Graphs 1 through 4 represent minimum root mean square r cancellation based on Model I

adjacent to point C are moved to locations more distant from this point

Figs 9 through 11 were computed after various modifications of Model I Only 7 instants of time at 12 msec intervals were considered the dipole vectors at these instants are depicted by solid rather than by dotted lines in Fig 1 Moreover the locations of the dipole at these instants of time *are not shown in Fig 1 but are* listed in Figs 9 through 11 The graphs illustrated in Figs 9 through 11 represent

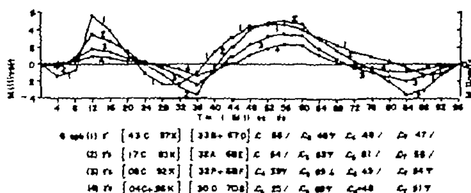


Fig 8 Graphs 1 through 4 represent minimum root mean square r cancellations based on Model II

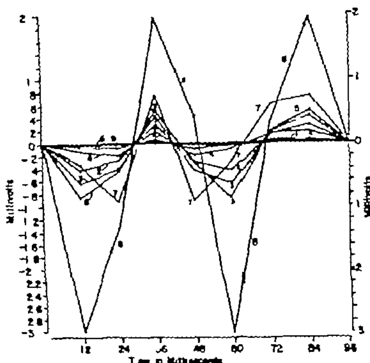
minimum range cancellations Although they are not illustrated minimum root mean square cancellations were also computed and their various coefficients are listed in the equations given within the brackets in Figs 9 through 11

For construction of Fig 9 the dipole migrates about the boundaries of three separate 2 cm squares The corners of these squares are formed by locations 02 22 20 and 00 for Graphs 1 through 3 by locations 24 44 42 and 22 for Graphs 4 through 6 and by locations 46 66 64 and 44 for Graphs 7 through 9 respectively Reference to Fig 1 shows that although the distance traversed by the migrating dipole is the same for these 3 groups of graphs the 2-cm square is located most centrally for Graphs 1 through 3 most peripherally for Graphs 7 through 9 and in an intermediate position for Graphs 4 through 6 Lead field theory[13] would indicate that the field of lead (C K) should become progressively less uniform as the 2 cm squares along the boundaries of which the dipole migrates assume progressively more peripheral locations This is confirmed in Fig 9 by the R cancellations of Graphs 1 4 and 7 which show increasing voltage deflections and also by their respective cancellation coefficients e g $C_1$ increases from 5 7 to 11 to 18 per cent

With the use of the same 4 points C G K and O in all instances both R and r cancellations were computed and are illustrated in Fig 9 As the uniformity of the field of lead (C K) decreases the R cancellations represented respectively by Graphs 2 5 and 8 demonstrate increasing voltage deflections and increasing cancellation coefficients e g $C_1$ increases respectively from 32 to 38 to 58 per cent In contrast as the lead field of (C K) becomes less uniform the r cancellations represented respectively by Graphs 3 6 and 9 show decreasing voltage deflections With such decreasing deflections the cancellaction coefficient $c_1$ decreases whereas the cancellation coefficients $c_3$ $c_4$ and $c_7$ remain approximately constant or increase

For Fig 10 the dipole migrates about the boundaries of three separate squares which measure 2 cm 4 cm and 6 cm along each side The corners of these squares are formed by locations 02 22 20 and 00 for Graphs 1 through 3 (identical with Graphs 1 through 3 of Fig 9) by locations 04 44 40 and 00 for Graphs 4 through 6 and by locations 06 66 60 and 00 for Graphs 7 through 9 respectively Location 00 is common for all three of these squares Lead field theory would indicate that lead (C K) should have a progressively less uniform field when the squares possess 2 cm 4 cm and 6 cm sides along which the dipole migrates This is confirmed in Fig 10 by Graphs 1 4 and 7 which show increasing voltage deflections and also by their respective cancellation coefficients e g $C_1$ increases from 5 7 to 18 to 35 per cent for Graphs 1 4 and 7 respectively

R and r cancellations were computed using the 4 points C G K and O and are illustrated in Fig 10 As the uniformity of the field decreases the R cancellations represented by Graphs 2 5 and 8 respectively demonstrate increasing voltage deflections and increasing cancellation co




Dipole Locations 02 at 12 12 at 24 22 at 36 21 at 48 20 at 60 10 at 72 00 at 84

Graph (1) R (C−K) [illegible] C₁ 7.4 C₂ 57% C₃ 0.3%
(2) R (C−K) [illegible] C₁ 32% C₂ 32.4 C₃ [illegible]
(3) r [illegible] (4.0+6.0) [illegible]

[R (C−K) [illegible] C₁ 6.2.4 C₂ [illegible] C₃ 0.4%
R (C−K) [illegible] C₁ 34% C₂ 35.4 C₃ [illegible]
r [illegible] (4.0+6.0) [illegible] 20%]

Dipole Locations 24 at 12 34 at 24 44 at 36 43 at 48 42 at 60 32 at 72 22 at 84

Graph (4) R (C−K) [illegible] C₁ 11% C₂ [illegible] C₃ [illegible]
(5) R (C−K) [illegible] C₁ 38% C₂ 38% C₃ [illegible]
(6) r [illegible] (4.0+6.0) [illegible] 20%

[R (C−K) [illegible] C₁ 17% C₂ 12% C₃ 1.3%
R (C−K) [illegible] C₁ 35.4 C₂ 40% C₃ 15%
r [illegible] (4.0+6.0) [illegible] 20%]

Dipole Locations 46 at 12 56 at 24 66 at 36 65 at 48, 64 at 60 54 at 72 44 at 84

Graph (7) R (C−K) [illegible] C₁ [illegible] C₂ [illegible] C₃ 3.3%
(8) R (C−K) [illegible] C₁ 64% C₂ 55% C₃ 30%
(9) r [illegible] (4.0+6.0) [illegible] 28% [illegible] 28%

[R (C−K) [illegible] C₁ [illegible] C₂ [illegible] C₃ 3.7%
R (C−K) [illegible] C₁ 67% C₂ [illegible] C₃ 37%
r [illegible] (4.0+6.0) [illegible] 28%]

Fig. 9 Only the seven solid line vectors of Fig. 1, those occurring at 12, 24, 36, 48, 60, 72 and 84 msec, are considered. The successive dipole locations are placed at various positions on the transverse plane so that the dipole migrates about three different 2-cm squares. Graphs 1 through 3 are based on the dipole migrating about the more centrally placed 2-cm square formed by locations 02, 12, 22, 21, 20, 10 and 00 at 12, 24, 36, 48, 60, 72 and 84 msec, respectively. Graphs 7 through 9 are based on the dipole migrating about the peripherally placed 2-cm square formed by locations 46, 56, 66, 65, 64, 54 and 44 at 12, 24, 36, 48, 60, 72 and 84 msec, respectively. Graphs 4 through 6 are based on the dipole migrating about an intermediately placed 2-cm square formed by locations 24, 34, 44, 43, 42, 32 and 22 at 12, 24, 36, 48, 60, 72 and 84 msec, respectively. Graphs 1, 4 and 7 representing R cancellations indicate that the field of lead (C−K) becomes less uniform as the 2-cm square assumes more peripheral locations. Graphs 2, 5 and 8 display R cancellations and Graphs 3, 6 and 9 display r cancellations. All of the graphs represent maximum range cancellations. Minimum root mean square cancellations were also calculated but are not illustrated by graphs. The data from the root mean square calculations are given within the brackets for comparison with the corresponding data obtained from the corresponding minimum range computations.

efficients, e.g., $C_1$ increases respectively from 32 to 79 to 99.8 per cent. The voltage deflections of the r cancellations show marked diminution in the case of the 4 cm. square (Graph 6) as compared with the 2 cm. square (Graph 3). The voltage deflections of the r cancellations with the 4 cm. and 6 cm. squares (Graphs 6 and 9, respectively) are approximately the same. The cancellation coefficients, designated as c, are similar for the 2 cm. and 4 cm. squares (13 and 15 per cent, respectively), whereas this coefficient is lower for the 6 cm. square (8.1 per cent). Cancellation coefficients c, $c_1$, and $c_2$ all increase for the 2 cm., 4 cm., and 6 cm. squares, respectively.

In practice, an R type of cancellation is usually carried out by combining 3 rather than 2 leads to cancel a fourth independent lead. The 3 leads are considered to be necessary because of the three-dimensional characteristics of the heart's electromotive forces. It was thought that it might be of interest to investigate how an extra degree of freedom may influence the cancellations obtained with a two-dimensional model. Accordingly, the study illustrated in Fig. 10 was repeated when a third lead (H K) was combined with leads (O K) and (G K) to cancel lead (C K) in accordance with Equation (5R). The results are depicted in Fig. 11. Graphs 1, 2, and 3 represent the minimum range R cancellations carried out when the dipole moves about the respective 2 cm., 4 cm., and 6 cm. sides of the three squares. These graphs should be compared, respectively, with Graphs 2, 5, and 8 of Fig. 10. It is noted that the contours of the cancellation deflections of Fig. 11 are markedly at variance with the corresponding graphs of Fig. 10. The cancellation coefficients of Fig. 11 are also smaller than the corresponding coefficients of Fig. 10. Moreover, the contribution of lead (G K) is completely reversed (for both R and R) as shown by the uniformly negative values of q in Fig. 11. Despite the fact that leads (H K) and (C K) are anatomically perpendicular, lead (H K) makes a greater contribution to the cancellation of lead (C K) than either lead (O K) or lead (G K). This is demonstrated in Fig. 11 by the fact that $q_2$ is numerically larger than either $q_1$ or $q_3$ for both R and R. These results raise the possibility that cancellation studies involving three degrees of freedom may introduce a factor which lowers the cancellation coefficient fortuitously. This point will be considered in greater detail in the *Discussion*.

**Discussion**

An R type of cancellation can be obtained from the time-varying voltages taken from the surface of a model (or from the body surface) without any knowledge of the nature of the internal generator. On the contrary, the calculation of an R type of cancellation from Equation (R) requires that the mean orthogonal components (X, Y, and Z) of the internally generated forces be known at each instant that a difference in potential is recorded with a surface lead. Thus, an R′ type of cancellation is not applicable to the study of the dipole property of the human heart. The terms x, y, and z of Equation (R) represent the constant components of the unique vector which minimizes the series of R voltages. For convenience, this vector will be referred to hereafter as the "uniform lead field vector." In the application of Equation (R) three degrees of freedom are involved, since x, y, and z may all assume values which are independent of each other. In contrast, the components x, y, and z of the image vector of a dipole location are not independent but dependent on the dipole location with respect to the lead in question. If such an image vector were substituted for the uniform lead field vector, Equation (R) would become

$$P' = P - Q(Xx + Yy + Zz) \qquad (R)$$

where the series of R voltages could be minimized by the optimal selection of the dipole location (fixing the values of x, y, and z) and by the determination of the optimal value for the coefficient Q, which remains constant at all instants of time. The minimized series of R deflections represents the "nonfixed dipole content" of lead I, that is, the voltage deflection which could not be obtained with a single equivalent dipole at a fixed but optimal location for this particular lead. If the volume conductor is infinite, a dipole location always exists which permits (Q Xx), (Q Yy), and (Q Zz) to be equivalent to (Xx′)

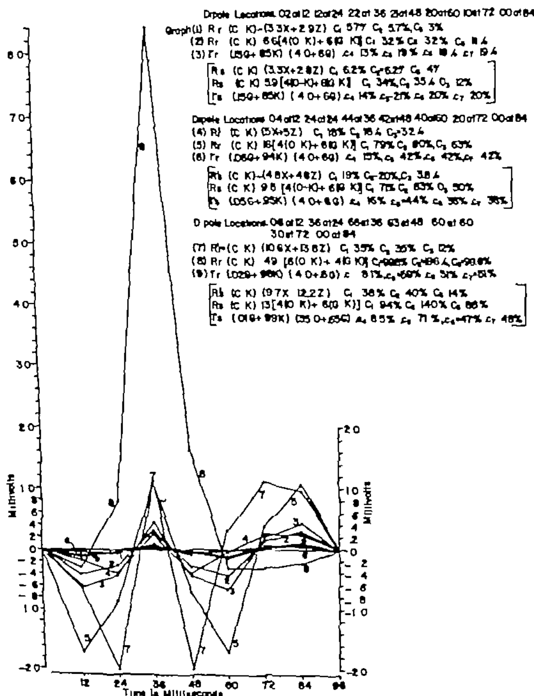



Fig. 10 As in Fig. 9 this illustration is also based on the same seven solid line vectors of Fig. 1. Graphs 1 through 3 are based on the dipole migrating about a 2-cm square formed by locations 0 1 ? 21 20 10 and 00 at 12 24 36 48 60 72 and 84 msec respectively. (Graphs 1 through 3 of Figs. 9 and 10 are identical.) Graphs 4 through 6 are based on the dipole migrating about a 4-cm square formed by locations 04 24 44 42 40 20 and 00 at 12 24 36 48 60 and 84 msec respectively. Graphs 7 through 9 are based on the dipole migrating about a 6-cm square formed by locations 06 36 66 63 60 30 and 00 at 12 24 36 48 60 72 and 84 msec respectively. Graphs 1 4 and 7 representing R cancellations indicate that the field of lead (C K) becomes less uniform as the squares assume a larger size. Graphs 5 and 8 represent I cancellation and Graphs 3 6 and 9 display cancellations. As in Fig. 9 only the minimum range cancellation are illustrated but data for minimum root mean square cancellation are given within the brackets for comparison with the corresponding minimum range data.

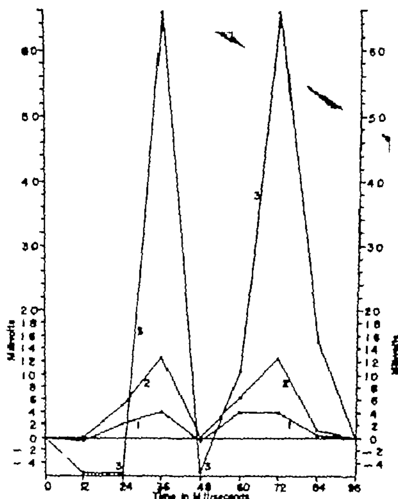



Fig. 11. The dipole locations forming 2-cm, 4-cm, and 6-cm squares are identical to those of Fig. 10. Graphs 1, 2 and 3 correspond to Graphs 2, 5 and 8 respectively of Fig. 10. In addition to the two leads (O K) and (G K) used in Fig. 10 to form the lead which cancels lead (C K), a third lead (H N) is combined with leads (O K) and (G K) to form the cancelling lead. Although lead (H N) is anatomically perpendicular to lead (C K), it makes a contribution to the cancelling lead which is larger than that of either lead (O K) or lead (G K) in all three cancellation graphs. This produces a considerable discrepancy between the cancellation coefficients and the contours of Graphs 1, 2 and 3 of Fig. 11 and Graphs 2, 5 and 8 of Fig. 10, respectively.

(Xy') and (Zz') respectively, so that R'' and R are identical. This equality results from the fact that the selection of the spatial dipole location involves three degrees of freedom which are unrestricted in an infinite spatial medium. If the volume conductor is finite, its boundaries restrict such a selection. A dipole location with an image vector having precisely the same direction as the uniform lead field vector need not then exist, in which case the minimized series of R' voltages obtained with

Equation (R′) exceeds the minimized series of R voltages obtained with Equation (R). In the present study, in which the moving dipole of Models I and II generates no Y forces, the (Q Yy) term of Equation (R′) is zero. If the transverse plane of Frank's model were infinite rather than bounded by the surface of the model as shown in the inserts of Figs. 3 and 4, the selection of a dipole location would involve two degrees of freedom without restriction, and (Q Xx) and (Q Zz) of Equation (R) could be made equivalent to (Xx′) and (Zz′), respectively, resulting in equality of R and R. However, as the result of the boundary of the transverse plane, this equivalency would not always occur since the fixed location of the single equivalent dipole is postulated to be on the transverse plane. Consequently, in the present report all of the graphs of minimized R voltages represent the content of lead (C K) which results from the nonuniformity of its lead field. The nonfixed dipole content of lead (C K) could be either identical with or somewhat larger than that indicated by the R voltages.

It is profitable to examine the studies of McFee and Parungao[13] in terms of the concept developed in the preceding paragraph. These authors utilized mathematical models consisting of either two or seven simultaneously functioning dipoles located in an infinite homogeneous medium. In the case of the model consisting of two dipoles, these were separated by a distance of 6 arbitrary units and an exploring unipolar electrode was located 9 units from the closest dipole along the line determined by the sites of the two dipoles. This line was oriented at equal angular distances from the orthogonal reference axes. In the case of the model consisting of seven dipoles, one was located centrally and the other six were arranged symmetrically so that each was located 4 arbitrary units from the central dipole, yielding a maximum dipole separation of 8 units. This model was studied with two different unipolar electrode placements. In one instance the unipolar electrode was located 12 units from the central dipole and in the other instance it was placed 24 units from the central dipole. *In both* instances the axis formed by the central dipole and the unipolar electrode was oriented at equal angular distances from the orthogonal reference axes.

The voltages of the unipolar electrode were cancelled by combinations of three leads referred to by the authors as x, y, and z heart vector leads oriented along the orthogonal reference axes. McFee and Parungao[13] state: "The voltages in the x, y, and z heart vector leads were proportional to the projection of the components of the electromotive forces in their direction and not dependent on the location of the electromotive forces." This statement implies that these voltages were calculated as though the image vectors for all the dipoles were orthogonal and of equal magnitude, that is, as though these leads possessed uniform lead fields. These authors[13] then state: "The voltage at the close exploring electrode did depend on the distance between this electrode and the various electromotive forces and proper allowance was made for this as well as for variations in the orientation of the different components of the different electromotive forces with regard to the exploring electrode." This statement implies that the voltages at the unipolar exploring electrode were calculated in accordance with the true magnitudes and orientations of the image vectors of the multiple dipoles. Consequently, the cancellation graphs can be interpreted as representing the content of the unipolar exploratory lead resulting from the nonuniformity of its field and, since the medium is infinite, this is equivalent to the nonfixed dipole content of this lead. McFee and Parungao[13] report a total of eight cancellations calculated to yield a minimum peak rather than a minimum peak-to-nadir excursion of the voltage deflections. The cancellation coefficients calculated as the ratio of the peak deflection of the cancellation voltage to the peak deflection of the voltage of the unipolar lead were 16 and 14 per cent for the two dipole model, 10, 17, and 17 percent for the seven dipole model with the close exploring electrode, and 7, 19, and 14 per cent for the seven dipole model with the more distant exploring electrode. McFee and Parungao did not consider that these relatively low coefficients expressed the nonfixed dipole content of the eight unipolar leads calculated from the multiple

dipole models. As an alternative, they compared in the same instances the voltages produced at the exploratory electrode by the two or seven dipoles with the voltages produced at the same electrode when the dipole sources of all of the electromotive forces were located at a single point at the centers of the models. They considered the discrepancy between the two graphs of these voltage deflections to represent the nonfixed dipole content or "proximity potentials" of the unipolar exploring electrode. It is the thesis of McFee and Parungao[11] that they have demonstrated that the voltages at a unipolar electrode *in close proximity to a number of separate dipoles* can contain substantial nonfixed dipole content and at the same time they can be efficiently cancelled by the voltages computed from a suitable combination of three orthogonal leads. It is our contention that their results do not support such a conclusion. As already *pointed out*, their cancellation graphs, calculated as minimum peak R cancellations, actually represent the nonfixed dipole content of the voltages at the unipolar exploring electrode. The superposition of the dipole sources of electromotive forces at a single central point is an unsatisfactory method of determining the maximum fixed single dipole content produced at the unipolar exploring electrode by the separate multiple dipoles. Such a central placement does not utilize the three degrees of freedom inherent in the selection of the optimal spatial location of an equivalent fixed dipole, since the components x, y, and z of the image vector of Equation (R ) thus become arbitrary constants which are completely unrelated to the constant components x, y, and z of the uniform lead field vector of Equation (R'). Moreover, the coefficient Q of equation (R ), which provides an additional and entirely justifiable means of maximizing the fixed single dipole content of a multiple dipole generator, is completely neglected. Finally, as the result of assuming uniform lead fields for their orthogonal leads, the cancellation coefficients of McFee and Parungao[11] are much lower than would have been obtained had the voltages of these leads been computed with regard to the true magnitudes and orientations of the separate multiple dipoles. The basis for this contention can be illustrated by Graphs 1 and 5 of Fig. 5 of this communication. Graph 1 represents the content of lead (C K) which results from the lack of uniformity of its field when the dipole migrates about the periphery of the 6 cm square. Graph 5 represents the cancellation of lead (C K) by the cancelling leads (O K) and (C K). If leads (O K) and (C K) had been assumed to possess uniform lead fields, which is the assumption made by McFee and Parungao[11] in connection with their orthogonal cancelling leads, Graph 5 would have been identical with Graph 1. Without this assumption, the cancellation *coefficient* $C_1$ *of Graph 5 is 94 per cent in* contrast to the much lower value of 37 per cent for $C_1$ of Graph 1. The exceedingly poor degree of cancellation represented by Graph 5 can be explained by the fact that the two cancelling leads (O K) and (C K) form lead 12 [4 (O K) + 6 (C K)], the *field of which diverges considerably from a* uniform lead field. Thus, an R cancellation calculated (but not illustrated) for lead 12 [4 (O K) + 6 (C K)] yields a value of 82 per cent for $C_1$, which exceeds by a considerable margin the corresponding coefficient of 37 per cent for the R cancellation of lead (C K) and indicates that the synthesized cancelling lead has much less uniformity of its field than that of the lead which it cancels.

If the location of the single dipole were stationary, all of the cancellation coefficients listed in Figs. 5 through 11 would be zero. On the contrary, as the result of migration of the dipole, cancellation coefficients of considerable magnitude are frequently obtained. Cancellations of the R type involving connections with four points on the surface of the transverse section will be considered first. The magnitudes of the R voltages of such a cancellation depend largely on the positions of the electrodes of the cancelling leads with respect to the positions of the electrodes of the lead being cancelled. For example, in the inserts of Figs. 3 and 4, if point K is a common electrode site of all three leads and if the two remaining electrodes of the cancelling leads approach as a limit the location at point C of the remaining electrode of the lead being cancelled, the resulting coefficients $C_1$, $C_2$ and $C_3$ will all approach zero as a limit. To

consider the other extreme, if the two remaining electrodes of the cancelling leads approach as a limit the location of the common electrode at point K, the cancellation coefficients $C_1$ and $C_3$ approach 100 per cent as a limit, whereas $C_2$ approaches 200 per cent. $C_1$ and $C_3$ have similar numerical values when R is relatively small but $C_2$ grossly exceeds $C_1$ when R is relatively large. When R is quite large, $C_3$ is only slightly lower than $C_1$. However, when R is relatively small, $C_3$ is considerably lower than $C_1$. Thus, if $C_1$ is 10 per cent (in which case $C_2$ would have a similar value), $C_3$ is only 1 per cent. This fact accounts in a large part for the apparent excellence of the cancellation coefficients calculated as (100 $C_3$) which Scher and his associates[9] obtained with factor analysis.

The graphs of the R cancellations displayed in Figs. 5, 6, 9, and 10 have cancellation coefficients which do not serve as adequate estimates of the corresponding coefficients of the R' cancellations. The R type of cancellation, however, can be utilized to determine the extent to which the deflections of any lead, precordial or otherwise, may be matched by the deflections of a lead derived from a vectorcardiographic reference system. This is of considerable practical importance in estimating the theoretical value of vectorcardiography. Okada, Langner, and Briller[3] used the x and z leads of Schmitt's SVEC III system[14] for cancelling a lead formed by an anterior chest electrode and a mid-back electrode placed at the same transverse level. They cancelled seven such leads with anterior chest electrodes located approximately at points A through G of the inserts in Figs. 3 or 4 on 19 normal individuals and on 6 patients with healed myocardial infarction, obtaining averaged $C_2$ coefficients of 23 and 29 per cent in the former and latter groups, respectively. These results exclude 1 additional normal subject and 2 additional patients with healed infarctions in whom $C_2$ values exceeding 60 per cent were obtained for two or more precordial sites. Okada and his associates carefully and rightfully point out that a cancellation coefficient gives the percentage of chest lead potential which is not recorded by the lead system in question and does not necessarily reflect the nonfixed dipole content of the chest lead since it is not valid to assume that the vectorcardiographic leads have completely uniform fields. Their use of only the x and z leads of the SVEC III system represented a conservative approach since they realized that the chest leads being cancelled were located approximately on the transverse or xz plane and would therefore possess only small y components. They compensated for such minimal y components by carrying out an apparently limited vertical search with the anterior chest electrode. If they had utilized all three leads of the SVEC III system, a spuriously low cancellation coefficient would have resulted whenever the y lead formed a major proportion of the three cancelling leads. Examples of spurious cancellations are illustrated in Fig. 11 of this paper, in which it is demonstrated that the introduction of a third cancelling lead into a basically two-dimensional situation may drastically change the configuration of the graph of the residual voltages and sometimes strikingly reduce the cancellation coefficient.

In another study published in abstract form, Briller and Okada[15] described the results of three-dimensional cancellations in which Precordial Leads $V_1$ through $V_6$ were each cancelled by a combination of three leads formed by the potentials of the right arm, left arm, and left leg, measured against the potential of an electrode on the back. They report mean cancellation coefficients (apparently $C_2$ values) which vary in the normal individuals from a maximum of 19 per cent for Lead $V_1$ to a minimum of 13 per cent for Leads $V_4$ and $V_5$, and in cardiac patients from a maximum of 38 per cent in Leads $V_1$ and $V_2$ to a minimum of 28 per cent in Lead $V_4$. In this study the *maximum* efficiency of the tetrahedral reference frame[16] in synthesizing precordial leads is presented. Since none of the three cancelling leads lie on the plane of the precordial leads being cancelled, the use of the three-dimensional technique may be justified. It should be realized, however, that such cancellations may involve spurious combinations of the three cancelling leads so that the lead fields of the synthetic leads and of the precordial leads may be considerably at variance.

Cancellations of the r type will be considered next. In the present study, the m and n coefficients of Equations 1r, 2r, 3r and 4r are varied, and the points on Frank's transverse plane designated by the various capitalized letters in these equations remain constant in location. This technique, which involves only two degrees of freedom, differs from that used by investigators who have reported cancellations of this general type performed on individuals with either normal or abnormal hearts.[1,7] In all of these studies, one electrode, designated as the search electrode, is moved in an unlimited manner from one location to another over the surface of the body. Only one of the coefficients, either m or n, depending upon which modified the potential of the search electrode, is varied. Such *techniques involve three degrees of freedom*, since movement of the search electrode over the two-dimensional surface of the body involves two degrees of freedom and the variation of one of the coefficients provides a third degree of freedom. It was noted that the graphs of r cancellation patterns illustrated in Figs. 7 through 10 show relatively small deflections. It is obvious that the addition of one more degree of freedom would further reduce the magnitude of these deflections.

As demonstrated in Figs. 9 and 10, the deflections of an r cancellation may decrease when a moving dipole migrates through a longer distance or is allowed to approach more closely a precordial electrode. Such paradoxical findings may be emphasized or reversed by the methods used to calculate coefficients for expressing the cancellations numerically. Thus, the coefficient $c_4$ may decrease as the nonfixed dipole content of the model increases. Since $c_4$ was utilized by Frank in his interpretation of multiple cancellations of the r type obtained from a single normal individual, his conclusion that the QRS complex recorded from any point on the body surface of his subject could be accounted for by an equivalent fixed dipole with an accuracy of about 5 per cent is unwarranted. Although the coefficients $c_5$, $c_6$, and $c_7$ increase as the nonfixed dipole content of the model increases, study of Figs. 9 and 10 indicates that there are no direct or predictable relationships between the graphs of R and those of r, and that neither $c_5$, $c_6$, nor $c_7$ yields any reliable information concerning the nonfixed dipole content of either of the models. Therefore, there is no justification for the contention of those investigators[1,3] who suggested that the accuracy of the single equivalent dipole representation of the heart could be quantitatively predicted from the $c_4$ coefficient, calculated from the cancellation of mirror patterns of normal and abnormal QRS complexes. On the other hand, Brody and his co-workers,[2,7] who utilized $c_4$ and $c_7$ in their studies, pointed out that cancellation techniques provide little detailed information concerning deviation of cardiac behavior from an equivalent fixed-location dipole. They cancelled both esophageal and right arm potentials with the potentials *of a variably located precordial electrode*, employing a four-electrode technique of the r type. They suggested that such a cancellation results in a null lead which is relatively insensitive to the electromotive forces of the heart despite its proximity to the esophageal and/or precordial electrodes. They also pointed out that deflections at any two instants during the cardiac cycle can always be completely cancelled and, therefore, that complete cancellation of the maximum positive deflection and maximum negative deflection of any lead is assured a priori. It is profitable to examine this latter concept from a mathematical standpoint as well as in the light of the results obtained in the present study. If n leads are used to form the cancelling lead of a minimum range cancellation, the upper (positive) limit of the cancellation graph may be formed by 1 to $(n + 1)$ points, and if there is more than one such point, all have the same potential. If the number of points forming the upper limit is m, the number of points forming the lower (negative) limit of the graph is $(n + 2) - m$; again, if there is more than one such point, all have the same potential. If the cancellation graph does not cross the zero (isoelectric) line, either the positive or the negative limit of the graph is formed by 1 to $(n + 1)$ points, and if this quantity, m, exceeds one, all have the same potential. There are then $(n + 1) - m$ potentials which are completely cancelled and are distributed as points along the zero line in addition to

the two zero end points These zero end points collectively may be considered to represent an additional single limiting point so that the number of points forming one limit of the graph at the zero line is actually $(n + 2) - m$ with the other limit being formed by 1 to $(n + 1)$ points thus the special case in which the cancellation graph does not cross the zero line has in reality the same number of upper and lower limiting points as the cancellation graph which crosses this isoelectric line one or more times (which may be as many as one less than the number of potential points between the zero end points) Except for those instances in which critical points limiting a minimum range cancellation are located on the zero line other potential points lying between the positive and negative limiting points do not have a zero value unless this occurs fortuitously Therefore the complete cancellation of the maximum positive deflection and the maximum negative deflection of a lead does not result in a minimum range cancellation

Fig 11 illustrates minimum range R cancellations in which the number of leads n forming the cancelling lead is 3 The total number of critical limiting points is therefore $(n + 2)$ or 5 Graph 1 demonstrates 3 positive points with equal potential and 2 negative points with equal potential In the case of Graph 2 there are 2 equal positive points and 2 points on the zero line between the zero end points which can be considered to represent a third zero point Graph 3 is limited by 2 equal positive points and 3 equal negative points In Figs 9 and 10 the R cancellations are produced by two cancelling leads so that the number of limiting potential points is $(n + 2)$ or 4 Likewise an r cancellation also has 4 limiting points since it is derived by rearrangement of terms from an R cancellation formed by two cancelling leads In the case of a two dimensional situation an R cancellation also has 4 limiting points since it can be considered to be analogous to an R cancellation formed by two cancelling leads In Figs 9 and 10 all of the minimum range R R and r cancellations are limited by 2 positive points with equal potential and 2 negative points with equal potential with the exception of Graph 8 of Fig 10 which is limited by a single positive point and 3 equal negative points Since the same number of critical limiting points and the same number of degrees of freedom are involved in achieving optimum R and r cancellations it is apparent that the great difference in the magnitude of the range of the respective R and r graphs cannot be explained on the basis of these factors Rather the differences between R and r graphs are dependent upon the differences in the lead fields of these two types of cancellation leads We agree with Brody and his associates[4,7] that the lead field of an r cancellation is essentially that of a null lead which records inherently low voltages

*The [illegible] more general description of the critical limiting points of a minimum range cancellation graph which does not cross the zero line than that which was given in the previous publication.[illegible]

## Summary and conclusions

The cancellation of an actual lead by a synthetic lead formed by combining two or three other leads cannot serve as an adequate index of the extent to which the heart can be represented by a single fixed location dipole Such a cancellation depends partially on the proximity of the electrode or electrodes of the actual lead to the electrodes of the leads forming the synthetic lead This type of cancellation (referred to in this communication as an R cancellation) can be used to determine the extent to which the deflections of any lead precordial or otherwise can be matched by the deflections of a lead synthesized from two or three orthogonal leads of a vectorcardiographic reference system If all of the leads of such a system are applied in the formation of the synthetic cancelling lead considerable care must be exercised in the interpretation of the cancellation pattern A spuriously low cancellation coefficient may be obtained if one vectorcardiographic lead contributes substantially to the formation of the synthetic lead when the lead being cancelled lies largely on the plane formed by the other two vectorcardiographic leads

An R cancellation is best evaluated quantitatively by the ratio in per cent of the magnitude of the cancellation residual to the magnitude of the cancelled lead Less satisfactory is the ratio in per cent of the magnitude of the cancellation residual to

the mean of the magnitudes of the cancelled lead and the synthesized cancelling lead this ratio exceeds 100 per cent when the cancellation residual is relatively large. The square of the ratio of the magnitude of the cancellation residual to the magnitude of the cancelled lead greatly overemphasizes the apparent excellence of any cancellation having a relatively small residual. This partially explains the inordinately good cancellation coefficients (98 per cent or higher) reported by investigators[1] who in effect subtracted this squared ratio from one and expressed the result in per cent by multiplying it by 100.

Mirror image cancellations (referred to in this communication as r cancellations) produce inherently low voltages so that their deflections are considerably smaller than those of R cancellations obtained with electrodes at identical locations. An r cancellation does not yield any reliable information concerning the accuracy of representing the heart as a single fixed-location dipole. In fact, our studies indicate that the deflections of an r cancellation sometimes diminish with an increase in the distance traversed by a single moving dipole. Moreover, some of the cancellation coefficients which have been applied to r cancellations may vary *inversely* with the magnitude of the deflections of the cancellation graph. Consequently, several published estimates of the percentage of nondipolar activity of the heart based on mirror image cancellations cannot be accepted as valid.

In the case of a model, a cancellation technique referred to herein as an R' cancellation can be used to demonstrate the minimized residual voltages of a lead resulting from nonuniformity of its lead field. If the model's conducting medium is infinite, the nonfixed dipole content of the lead based on the optimal location of a postulated single dipole is identical with that resulting from lack of lead field uniformity. If the model's medium is bounded rather than infinite, these two quantities may or may not be identical; the nonfixed dipole content may be somewhat larger but can never be smaller. Utilizing models of multiple dipoles within an infinite medium, McFee and Parungao published cancellation graphs which were actually R' cancellations. McFee and Parungao did not consider that their cancellation graphs represented the nondipolar contents of their leads; for these estimates they used another computational technique which a priori would be expected to produce larger residuals than the minimized residuals of the R' cancellations. Their data do not justify their conclusion that the voltages at a unipolar electrode in close proximity to a number of separate dipoles can contain substantial nonfixed dipole content and at the same time can be efficiently cancelled by voltages formed by a suitable combination of orthogonal leads. If the voltages of their orthogonal leads had been dependent upon not only the magnitudes and orientations but also the locations of the separate dipoles, they would have computed R rather than R' cancellations. Cancellation coefficients of the R type were always substantially larger than those of the R' type in our own studies except in one instance (exemplified by Graphs 1 and 7 of Fig. 6) which resulted from proximity of the precordial electrodes of the cancelling leads with the precordial electrode of the lead being cancelled. This condition would not have obtained in any of the experiments of McFee and Parungao. Had they calculated R cancellations as well as R' cancellations, they would have found that the former, representing the type of cancellation which can be performed experimentally on human subjects, would have been substantially larger than the R' cancellations which they illustrate. Since an R' cancellation represents the nonfixed dipole content of the cancelled lead when the medium is infinite, their studies would then have agreed with our conclusion that an R cancellation usually grossly overestimates rather than underestimates the degree of nondipolarity of a lead.

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# Present status of the concept of oxygen differential in the etiology of ventricular fibrillation after coronary occlusion

*Henry S. Badeer, M.D.**
*Brooklyn, N. Y.*

In a recent symposium on "Sudden Cardiac Death" held at the University of Kentucky Medical Center, the view was expressed that the role of "oxygen differential" in the pathogenesis of ventricular fibrillation (VF) after coronary occlusion is a subject of controversy.[1] At the same symposium, in reply to a query on Beck's concept of oxygen differential, Harris[2] stated that in acute coronary occlusion ventricular ectopic beats (hence VF), which are said to arise at the boundary between oxygenated and nonoxygenated cardiac tissue, are due to the outpouring of potassium from the ischemic muscle cells. In his opinion, local potassium diffusion *gradients* were essential for the production of ventricular arrhythmias soon after coronary artery occlusion.

The purpose of this communication is to outline briefly the concept of oxygen differential as proposed by Brofman, Leighninger, and Beck[3] in 1956 and to present the experimental data that have accumulated since then for or against the hypothesis. Although I have reviewed the pathogenesis of VF soon after coronary occlusion in a recent article,[4] I think that a more detailed discussion of the concept of oxygen differential is warranted because of its wide acceptance and also because of the fact that additional data have accrued since the above-mentioned review was written. It must be made clear that this analysis will be limited to VF that supervenes soon after experimental coronary occlusion (within 1 hour in dogs). It will not deal with the mechanism of delayed arrhythmias (ventricular ectopic beats or ventricular tachycardia) that develop 4 to 8 hours after a two-stage coronary artery ligation in dogs, persist for 2 to 4 days, and then disappear spontaneously.[5]

For the details of the concept of oxygen differential the reader is advised to consult Beck's paper.[3] In brief, it stated that ventricular ectopic activity (hence VF) originates from currents that are set up between ischemic and well-perfused regions of the ventricular myocardium because of the marked *difference in the oxygen tension* (concentration) that follows rapidly the occlusion of a major coronary artery. Impulses are believed to arise at the boundary zones. The size of the vessel (hence the mass of ischemic muscle) is important in reaching the threshold intensity of current that causes ectopic activity and fibrillation. It is also implicit in the concept that the greater the oxygen differential, the greater will be the intensity

Received for publication Nov. 29, 1965.
*Visiting Professor, Department of Physiology, State University of New York Downstate Medical Center, 450 Clarkson Ave., Brooklyn, N. Y. 11203.

of the current and the likelihood of reaching the fibrillation threshold. The essential observation that led to this hypothesis was that in contrast to coronary occlusion, acute fatal hypoxic hypoxia or asphyxia in the dog practically never caused VF. The heart became diffusely cyanotic, dilated, and within a short period stopped beating (asystole).[3,4] Absence of fibrillation was attributed to the uniformity of anoxia in the myocardium. Although this observation has been repeatedly confirmed by others, it has been contradicted by Coffman and Gregg,[7] who reported terminal VF in some dogs (particularly large size dogs) killed by asphyxia. On careful analysis it may be noted that VF in Gregg's experiments was detected only by electrocardiography, and that it occurred about 15 minutes after blood pressure dropped to near zero. This is not comparable to the VF that follows coronary occlusion in which ectopic activity and VF occur when the heart is still pumping fairly adequately. A similar argument has also been advanced by Beck.[4] The absence of VF has been noted also in acute fatal hemorrhage.[4] Here too marked oxygen differentials are lacking. Coronary blood flow declines gradually throughout the *entire* myocardium and cardiac anoxia is diffuse.

Another interesting observation of Beck in support of his concept is that in an asphyxiated animal in which the heart is still beating, perfusion of one of the major coronary arteries with *oxygenated* blood may induce VF (so-called "reverse trigger").[4]

Many workers including Beck have presented electrographic data to indicate differences in potential between ischemic and well perfused areas of the myocardium. However, there is no evidence that these currents originate from the *differential in oxygen*. In fact, Warren, Saurbrey, and Wandall[9] have shown that the injury currents develop in the absence of significant differences in oxygen content between occluded and nonoccluded areas. In my opinion the view that oxygen differential is responsible for these currents appears to be the weakest argument in the hypothesis of Beck. Besides, it is not certain that these differences in potential set up pacemaker activity in the ventricles.

In 1959 Badeer and Horvath[10] attempted to test the hypothesis of Beck by other means. It was thought that if the concept of oxygen differential is correct, arrest of the *entire* coronary arterial blood flow to the myocardium should not induce VF but stop the heart in asystole. This procedure in dogs almost invariably led to VF soon after occlusion. On the basis of this, serious doubts may be raised about the importance of large *differentials* in the myocardium, not only in oxygen concentration and electrical potential but also in potassium concentration as postulated by Harris.[3,11] However, it does not rule out the possible role of the release of potassium from ischemic cells in the initiation of ectopic activity.

In 1962 Danese[12] approached the problem in another way. He perfused the circumflex branch of the left coronary artery in dogs with homologous serum for a period of 1 hour and noted that in none of the 10 dogs did VF occur, whereas in a control series occlusion of the circumflex artery caused VF in 60 per cent of the dogs. It was assumed in these experiments that perfusion of the circumflex artery with serum created a large oxygen differential between the serum and blood perfused regions of the myocardium. In line with these findings are the observations of Petropoulos[13] who perfused in dogs the anterior descending coronary artery with mixed venous blood obtained from the right atrium of donor dogs (oxygen content = 13 volumes per cent) for a period of 30 minutes and followed this by 6 per cent dextran in saline for another 30 minutes. He observed no fibrillation in 10 experiments.

In 1962 I used still another method to test Beck's hypothesis.[14] It was reasoned that in coronary occlusion the oxygen differential could be increased by the inhalation of 100 per cent oxygen, and if the concept of oxygen differential is correct, this procedure should favor ectopic activity and VF. In 25 experiments on anesthetized open-chest dogs it was found that the incidence of VF within a period of 1 hour after ligation of the anterior descending coronary artery in animals breathing 100 per cent oxygen was 28 per cent, whereas in a series of 25 control dogs

breathing room air the incidence was 20 per cent. The difference was not statistically significant. In this study the oxygen differentials were not measured, but Siven and associates[1, 14] have shown by the polarographic method that inhalation of 100 per cent oxygen increased the $pO_2$ by 50 to 200 per cent or more in perfused regions of the ventricular myocardium, whereas in ischemic areas there was hardly any rise at all. These experiments were significant not only in testing Beck's hypothesis but also in evaluating the possible hazards of administering oxygen to patients with acute myocardial infarction.

The investigations of Warren and co-workers[9] showed that the pattern of "injury" as recorded by the epicardial electrogram was unrelated to the oxygen differential between ischemic and nonischemic areas. This was demonstrated by producing generalized hypoxia (inhalation of 4 per cent oxygen) and simultaneously occluding a coronary artery or releasing the occlusion during hypoxia. From these studies they concluded that the difference in oxygen concentration of ischemic and nonischemic areas of the myocardium was not responsible for the "current of injury" and VF in experimental coronary occlusion in the dog.

In this connection, reference should be made to the observations of Jacobson, Schiess, and Moe.[1] These investigators noted that exposure to concentrations of oxygen between 5 and 10 per cent in the inspired air in unanesthetized dogs exhibiting *delayed ventricular tachycardia* (1 to 3 days after a two-stage coronary occlusion) reduced the frequency of discharge of the ectopic ventricular focus. At first sight this may be taken to support the concept of oxygen differential, but a closer analysis shows that Moe's studies were concerned with *delayed* ventricular tachycardia, which rarely terminates in VF, whereas Beck's concept pertains specifically to *early* ventricular ectopic activity (within 1 hour after occlusion in dogs), which often terminates in VF. In the former case, necrosis of tissue with microscopic changes is a prominent feature, whereas in the latter the changes are essentially electrochemical with no microscopically detectable alterations. Furthermore, hypoxic hypoxia alters so much of cell physiology that the reduction in arrhythmia may be related not necessarily to the decline in "oxygen differential" per se but to almost any of the metabolic changes that occur.

Finally, the experimental data of Chardack and associates[18] may be significant with respect to the concept of oxygen differential. These workers reported that a progressive increase in the $pO_2$ of the inspired air by the inhalation of 100 per cent oxygen at 1 atmosphere, 2 atmospheres, and 4 atmospheres (absolute) tended to *reduce* the incidence of VF in anesthetized dogs in which the circumflex coronary artery was ligated. More striking beneficial results were reported by Smith and Lawson[19, 20] in dogs subjected to 100 per cent oxygen at 2 atmospheres (absolute) pressure. According to Beck's concept, one expects that the markedly increased oxygen differential would increase the incidence of VF. On the contrary, if anything, it tends to decrease it. The situation is somewhat complex because, although the oxygen differential and oxygen gradient are markedly increased, the mass of ischemic tissue may be diminished under these circumstances by an improvement in the oxygen available to the tissue at the boundary. Since the mass of ischemic tissue plays a role in attaining the threshold value for ectopic activity and VF, this may be the basis for the beneficial tendency of hyperbaric oxygen.

In summary, it may be stated that all of the results of experimental studies carried out since the concept of "oxygen differential" was proposed in 1956 speak against the importance of oxygen differentials in the etiology of VF soon after acute coronary artery occlusion. The pathogenesis of ventricular fibrillation after coronary occlusion remains uncertain, and the reader may benefit from a recent review on the subject.[4] Analysis of experimental data available to date suggests that the mechanism may involve a disturbance in myocardial cell metabolism and membrane properties related not so much to a *lack of oxygen* but rather to the *arrest of flow of plasma* (absence of perfusion) to a large mass of contracting myocardium. Whether it is the absence of

a substance(s) brought by the plasma or it is the removal of a metabolic product(s) by the plasma or both is unknown. It seems to be more likely that ectopic activity is related to an excessive accumulation of a metabolic product(s) that alters membrane properties. The absence of ventricular arrhythmias and VF in acute fatal hypoxic hypoxia asphyxia or hemorrhage may be a question of the *degree of accumulation (hence the concentration)* of such a product(s) since in all of these conditions the coronary blood flow persists (although progressively curtailed) until all mechanical activity of the myocardium ceases. This flow may wash away the metabolic products and reduce their concentration below threshold levels. Ischemic nonischemic boundaries in the ventricles do not seem to be essential for ectopic activity.

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# The effects of morphine on the resistance and capacitance vessels of the peripheral circulation

*R. Peter Henney, M.D.,**
*John S. Vasko, M.D.*
*Robert K. Brawley, M.D.*
*H. Newland Oldham, M.D.*
*Andrew G. Morrow, M.D.*
*Bethesda, Md.*

Since its isolation and description over a century ago morphine has remained one of the most valuable drugs available to the physician. Morphine is commonly administered to patients with acute cardiovascular disorders such as shock, pulmonary edema, or myocardial infarction, and it is surprising that so little meaningful information is available concerning its effects on the heart and circulation. Many studies of the pharmacologic actions of morphine on the peripheral vascular system have been reported, and although the results of these studies are conflicting, the majority indicate that morphine has some dilating effect on peripheral vessels. In most investigations, however, no attempt was made to separate the cardiac effects of the drug from its peripheral ones, and the depressed respiration of the morphinized animal was usually not taken into account.[1-4]

Previous explanations of the effects of morphine on the vascular system were largely based upon classic concepts of the mechanisms of regulation of the peripheral circulation and these in turn were largely concerned with the function of resistance vessels. It is now appreciated, however, that 60 to 80 per cent of the circulating blood volume is contained within the peripheral venous system, and that this vascular bed is highly reactive and able to alter its capacity in response to a wide variety of physiologic and pharmacologic stimuli. In the capacitance vessels large changes in volume are associated with relatively small alterations in pressure, and valid measurements of capacitance are possible only when the effects of cardiac contraction and respiration on venous pressure are eliminated. In this laboratory the effects of morphine on ventricular performance were assessed in intact dogs in which the heart was separated from the peripheral circulation by appropriate cardiopulmonary bypass techniques.[5] Similar methods were employed in the present experiments concerning the effects of morphine on the resistance and capacitance vessels of the peripheral circulation.

From the Clinic of Surgery, National Heart Institute, Bethesda, Md.
Received for publication Dec. 1, 1965.
*Address: Clinic of Surgery, National Heart Institute, National Institutes of Health, Bethesda, Md. 20014.

## Methods

Mongrel dogs ranging in weight from 18 to 30 kilograms were anesthetized with intravenous chloralose (60 mg per kilogram) and ventilated through a cuffed endotracheal tube with a volume controlled piston respirator supplying room air. A bilateral transverse thoracotomy was performed and heparin (3 mg per kilogram) was administered intravenously. Systemic arterial and central venous pressures were measured through polyethylene catheters inserted into the abdominal aorta and vena cava from the femoral artery and vein respectively. The catheters were connected to Statham p23Db transducers which were calibrated before each experiment with a water manometer. The zero or base line reference for all pressures was the level of the right atrium, and recordings were made with a photographic or direct writing oscillograph. Body temperature was monitored with an esophageal thermistor and was maintained at 36 to 37.5°C with a heat exchanger when cardiopulmonary bypass was employed. The pH of arterial blood was measured frequently during each experiment and remained between 7.35 and 7.45 in all animals.

The experimental methods utilized to assess changes in vascular resistance and capacitance were similar to those used by Ross and associates[1] in studies of the digitalis glycosides. The extracorporeal circuit was primed with a 2:1 mixture of Ringer's lactate solution and dextran; the priming volume was similar to the estimated blood volume of each animal and during bypass approximately 50 per cent hemodilution resulted. No homologous blood was administered, since in the dog it is a well recognized cause of venous pooling.[9] All venous blood was drained from the right heart directly into a rotating disc

Fig. 1. Schematic representation of the cardiopulmonary bypass circuit utilized in the determinations of total peripheral arterial resistance and the capacity of the peripheral vascular compartment. In all experiments systemic blood flow was maintained constant and was constantly monitored by an electromagnetic flowmeter in the arterial return line. Venous blood was returned from the right atrium (RA) and right ventricle (RV); the pulmonary artery (PA) was occluded. Blood was returned from the oxygenator to the femoral artery (FA). Pressures were measured by means of pressure transducers (SG) attached to catheters inserted through the femoral artery and femoral vein (FV). In the determinations of capacitance, venous return was also measured by a flowmeter in the venous return line and changes in blood volume were determined by the volume which was withdrawn from the calibrated reservoir (RES) to restore the blood level in the oxygenator to the control one.

oxygenator and arterialized blood was returned to the femoral artery at a constant rate through a calibrated totally occlusive pump (Fig. 1). The transducer of an electromagnetic flowmeter (Statham E 3000) was inserted into the arterial return line and systemic arterial flow was constantly monitored. Flow rates ranged from 58 to 91 ml. per kilogram per minute and averaged 76 ml. per kilogram per minute. After the institution of cardiopulmonary bypass a short period of circulatory stabilization was allowed and control measurements were then made. Morphine (1 mg. per kilogram) was rapidly injected into the blood passing through the oxygenator and continuous observations were made during the subsequent 30 minute period.

*Effects of morphine on resistance vessels.*

A. Thirteen dogs were studied during total cardiopulmonary bypass. Systemic arterial pressure and central venous pressure were recorded before and continuously for 30 minutes after the administration of morphine while systemic arterial flow remained constant. Total peripheral vascular resistance (TPR) was calculated from the following formula and expressed in dynes sec. cm.:

$$TPR = \frac{(MAP - MCVP) \times 980}{Flow}$$

Where MAP = mean arterial pressure cm. $H_2O$, MCVP = mean central venous pressure cm. $H_2O$, Flow = systemic arterial flow ml./sec., and 980 = conversion factor from cm. $H_2O$ to dynes cm.[2]

B. In 3 additional dogs heparin was administered and two cannulae were introduced into the left common femoral artery, one directed proximally into the aorta and the other distally for 1 to 2 cm. Both cannulae were introduced into the artery through a single longitudinal incision; the artery was not divided. Arterial flow into the femoral artery was then controlled by an occlusive finger pump which perfused the distal artery with blood from the aorta. Arterial pressure was recorded from a small distal branch of the left femoral artery and central aortic pressure was simultaneously measured from a catheter inserted from the right femoral artery. The flow into the left femoral artery was adjusted until the mean femoral arterial pressure was identical to the mean aortic pressure. Morphine (0.5 mg. per kilogram) was rapidly injected into the perfused left common femoral artery as the pressures were continuously recorded.

*Effects of morphine on capacitance vessels.*

A. The extracorporeal system previously described (Fig. 1) was utilized with certain modifications for assessment of the effects of morphine on the volume of the total systemic vascular compartment. In 12 dogs total bypass was instituted and, after the stabilization period, 300 to 500 ml. of the completely mixed blood and priming solution were withdrawn from the circuit into a calibrated reservoir. The blood level in the oxygenator was then recorded and morphine (1 mg. per kilogram) was rapidly injected into the blood within the oxygenator. An increased vascular capacity was reflected in a fall in the blood level in the oxygenator, and this volume was measured as it was replaced from the reservoir. In 2 of the 12 dogs portal venous pressure was also recorded from a catheter inserted into the portal vein at prior laparotomy. Changes in blood volume were recorded over a 30 minute period. In 3 additional animals an intravascular flow transducer (Medicon QH 2100 c) was inserted into the line returning venous blood to the oxygenator and the instantaneous changes in venous return were recorded after the administration of morphine.

B. Venous tone was determined in 8 animals by the major vessel occlusion technique described by Bartelstone.[10] After bilateral thoracotomy the azygos and highest intercostal veins and both internal mammary arteries and veins were ligated. The circulation to the lower half of the body was isolated by simultaneous occlusion of the inferior vena cava and descending thoracic aorta immediately above the diaphragm. Venous tone was expressed in cm. $H_2O$ as the difference between control pressure in the inferior vena cava and the pressure recorded 30 seconds after the occlusion. Determinations of venous tone were made before and at intervals of 5 to 15 minutes after the intravenous injection of morphine (0.5 mg. per kilogram). In these experiments the drug was administered slowly over a period of 30 seconds and

only modest changes in systemic arterial pressure resulted

**Results**

*Effects of morphine on resistance vessels*

A In each of the 13 dogs studied during cardiopulmonary bypass total peripheral vascular resistance decreased after the administration of morphine (Table I) In this experimental preparation arterial flow was constant and the systemic arterial pressure varied directly as peripheral resistance A precipitous fall in systemic pressure occurred 30 to 90 seconds after injection of the drug and the pressure was lowest 3 to 5 minutes after injection the time at which the data in Table I were recorded The total peripheral vascular resistance in the control period varied among individual animals (1 400 to 6 200 dynes sec cm⁻⁵) but was always lower after morphine the maximum decreases in resistance ranged from 11 to 79 per cent of control values and the average decrease was 46 ± 20 per cent (± 1 S D) The reduced pressure (resistance) persisted for 5 to 6 minutes after which time the pressure gradually rose and approximated the control level 20 minutes after the injection (Fig 2) In all dogs the pressure had returned to the initial level by 30 minutes and in 7 animals it was higher than the control value at this time

B The changes in pressure recorded in the perfused femoral artery and the aorta after the injection of morphine into the femoral artery were similar in each of the 3 animals and representative records from one experiment are reproduced in Fig 3 After the injection the pressures in both the femoral artery and the aorta remained unchanged for 20 to 30 seconds then fell simultaneously The fall in femoral arterial pressure did not occur immediately but only after a delay during which it was possible for the injected drug to reach the central circulation These observations indicate that morphine had no direct effect on resistance in the vascular bed supplied by the femoral artery

*Effects of morphine on capacitance vessels*

A Significant increases in the capacity of the total systemic vascular compartment were noted in each of 12 dogs after the administration of morphine The volume of blood in the oxygenator rapidly decreased 45 to 90 seconds after injection of the drug reflecting increases in the total blood volumes of the animals The increases in blood volume ranged from 4 5 to 26 ml

*Table I Total peripheral vascular resistance before and 5 minutes after administration of morphine (1 0 mg /Kg )*

| Animal number and weight (Kg) | Systemic arterial flow (ml/min) | Mean arterial pressure (cm H₂O) | | Mean venous pressure (cm H₂O) | | Total peripheral vascular resistance (dynes sec cm⁻⁵) | | % Change in total peripheral vascular resistance |
|---|---|---|---|---|---|---|---|---|
| | | Before morphine | After morphine | Before morphine | After morphine | Before morphine | After morphine | |
| 1 (21) | 1 450 | 125 | 100 | 4 | 4 | 4 900 | 3 808 | −21 |
| 2 (20) | 1 380 | 65 | 55 | 4 | 3 | 2 270 | 1 940 | −15 |
| 3 (25) | 2 000 | 163 | 65 | 4 | 2 | 4 740 | 1 860 | −61 |
| 4 (2 ) | 2 000 | 107 | 35 | 7 | 3 | 2 740 | 940 | 66 |
| 5 (26) | 1 900 | 95 | 50 | 4 | 3 | 2 870 | 1 450 | −48 |
| 6 (19) | 1 570 | 90 | 55 | 3 | 8 | 3 3 0 | 1 870 | −46 |
| 7 ( 1) | 1 650 | 40 | 10 | 2 | 1 | 1 350 | 370 | − 6 |
| 8 (30) | 2 200 | 100 | 50 | 5 | 5 | 2 540 | 1 200 | −53 |
| 9 (18) | 1 500 | 90 | 55 | 1 | 0 | 3 490 | 2 160 | −35 |
| 10 (23) | 1 140 | 135 | 130 | 4 | 4 | 4 60 | 4 2 0 | −11 |
| 11 ( ) | 1 870 | 135 | 80 | 1 | 1 | 4 340 | 2 560 | −41 |
| 1 (19) | 1 050 | 115 | 25 | 3 | | 6 210 | 1 790 | − 9 |
| 13 (22) | 1 500 | 0 | 45 | 3 | 3 | 2 520 | 1 6_0 | −37 |
| | | | | | | Mean ± 1 S D | | −46 ± 20 |

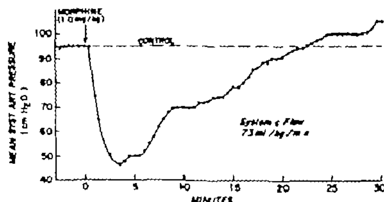



Fig 2 Representative effects of morphine (1 0 mg /kg ) on total peripheral vascular resistance in one animal Since the total systemic blood flow was maintained constant resistance varied directly as the mean systemic arterial pressure Pressure (resistance) fell immediately after morphine was given and the effect was most pronounced after 3 to 4 minutes Thereafter the pressure gradually rose approximated the control value at 20 minutes and exceeded it at the end of the 30-minute period of observation

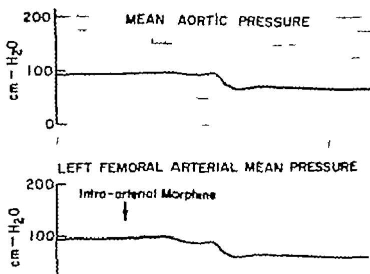



Fig 3 Records of mean pressure recorded in the central aorta and in the perfused left femoral artery before and after the intra arterial injection of morphine into the perfused vascular bed The fall in pressure in the femoral artery occurred simultaneously with that in the aorta indicating that morphine had no direct effect on resistance but acted on the perfused bed only after it had reached the central circulation and caused a general fall in resistance as reflected in the decline in aortic pressure

per kilogram and averaged *11 ± 6 ml* per kilogram Expressed in another manner the estimated blood volumes of the individual dogs (7 per cent of body weight) increased 6 to 38 per cent and the average increase was 17 ± 9 per cent Systemic venous return *measured with a flowmeter* in 3 dogs rapidly decreased after the injection Venous return then slowly increased until it again equaled systemic arterial flow after approximately *5 minutes* (Fig 4) The volumes of blood in the animal and in the extracorporeal circuit remained stable after the initial shift and during the 30 minute period of observation the blood originally taken up by the animal *was not returned to the oxygenator* indicating that the increased capacity of the vascular compartment persisted for at least this period of time In both dogs in

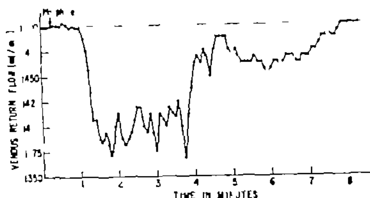



Fig. 4. Instantaneous measurements of systemic venous return recorded from an electromagnetic flowmeter in the venous return line of the extracorporeal circuit before and after the rapid intravenous administration of morphine (1.0 mg./Kg.). Systemic blood flow remained constant throughout the period of observation. An abrupt decrease in the volume of venous return occurred immediately after the drug was given and then slowly rose until it again equaled systemic arterial flow after approximately 5 minutes. During the period of observation, however, the blood taken up by the animal was not returned to the oxygenator and increased capacity of the vascular compartment persisted during this time. In this experiment, the volume of blood pooled, indicated by the integrated area of the flow curve, was 404 ml.

which it was measured, portal venous pressure fell 15 to 30 seconds after the administration of morphine and remained below the control level for 30 seconds in one animal and for 2 minutes in the other. The decreases in portal venous pressure were simultaneous with those in arterial pressure and venous return, and portal venous pressure was low or normal in both dogs when maximum pooling had occurred. In one animal, portal venous pressure remained normal throughout the remainder of the observation period, whereas in the other a transient increase with a maximal pressure 4 cm. $H_2O$ above control was observed between the fifth and tenth minutes after injection.

B. Venous tone determined by major vessel occlusion ranged from 5.3 to 9.5 and averaged 6.8 ± 1.3 cm. $H_2O$ in the 8 dogs under control conditions (Table II). After the administration of morphine, venous tone fell in every animal (Fig. 5) and the average value determined 5 to 15 minutes after injection was 3.5 ± 1.1 cm. $H_2O$ ($p < .01$). Serial measurements during the remainder of the observation period indicated no significant change in venous tone, and the decrease persisted for at least 30 minutes. The decreased vena caval pressure during major vessel occlusion observed in every animal after morphine cannot be related to effects of the drug on resistance vessels, since it has been demonstrated that the venous system is isolated from influences of the arterial circulation during the period of occlusion.[10] The mean arterial pressure was lower after the administration of morphine in 7 of the 8 dogs, but the decreases were modest, and the average change was only −14 cm. $H_2O$.

## Discussion

The present studies demonstrate that in the dog the intravenous administration of morphine results in an immediate and significant decrease in total peripheral vascular resistance. Morphine also increases the capacity of the total peripheral vascular compartment, and the observed decreases in venous tone indicate that the increased volume of blood is largely contained within capacitance vessels. The investigations do not, however, provide conclusive information as to whether the increased capacitance is effected by dilatation throughout the venous system or whether it is the net result of different actions of morphine upon the portal and systemic venous beds. Ross, Braunwald, and Waldhausen[8] found that venous pooling occurred after the administration of digitalis glycosides, but demonstrated that pooling did not result from venodilation

*Table II. Venous tone determined by the major vessel occlusion technique of Bartelstone and mean arterial pressure before and 5 to 15 minutes after administration of morphine (0.5 mg./Kg.)*

| Animal | Mean arterial pressure (cm. $H_2O$) | | Venous tone (cm. $H_2O$) | | % Change in venous tone |
|---|---|---|---|---|---|
| | Before morphine | After morphine | Before morphine | After morphine | |
| 1 | 130 | 115 | 5.5 | 2.0 | −64 |
| 2 | 110 | 100 | 7.7 | 3.8 | −51 |
| 3 | 115 | 95 | 6.0 | 2.0 | −67 |
| 4 | 125 | 125 | 9.5 | 4.5 | −53 |
| 5 | 125 | 105 | 6.7 | 5.2 | −22 |
| 6 | 105 | 90 | 7.5 | 5.0 | −33 |
| 7 | 135 | 120 | 6.5 | 3.0 | −54 |
| 8 | 100 | 80 | 5.3 | 2.3 | −57 |
| Mean (± 1 S.D.) | 118 | 104 | 6.8 ± 1.8 | 3.5 ± 1.1 | −50 ± 15 |

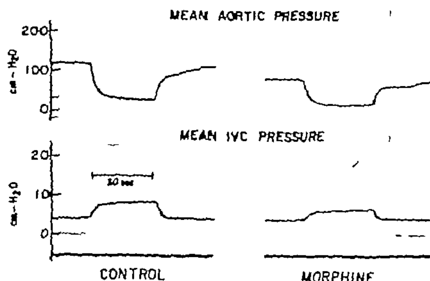



Fig. 5. Records of mean aortic and inferior vena caval (IVC) pressures recorded before, during, and after a 30 second period of major vessel occlusion (Bartelstone). Venous tone, expressed as the difference in the IVC pressure before and at the end of the 30-second period of occlusion, decreased from a control value of 4.5 cm. $H_2O$ to 3.0 cm. $H_2O$ at 10 minutes after morphine had been administered intravenously.

but principally from hepatic venoconstriction and an increase in splanchnic blood volume. In the present experiments changes in volume were not measured separately in the portal and systemic venous beds. The fact that a rise in portal venous pressure did not accompany the increase in blood volume would suggest, however, that hepatic venoconstriction played no important role in the venous pooling observed after the administration of morphine.

The different durations of the changes in vascular resistance and capacitance induced by morphine are worthy of comment. Total peripheral vascular resistance fell immediately after morphine was administered

but in all animals normal or even increased resistance was noted within 30 minutes. Morphine also had an immediate effect on the capacitance vessels but these changes persisted throughout this same period of time. In previous studies morphine was shown to improve left ventricular performance and to increase myocardial contractile force.[7] These positive inotropic effects gradually increased after the administration of morphine and were maximal at the end of a 30-minute period of observation. These actions of morphine on the heart were considered to be indirect ones and were attributed to sympatho-adrenal discharge since they did not occur after adrenalectomy or beta adrenergic blockade. Accordingly, it might be postulated that the release of vasoactive substances from the adrenals and/or the sympathetic effectors was responsible for the progressive increase in peripheral vascular resistance which followed the initial decrease. Such a mechanism might have been expected to produce a corresponding gradual decrease in capacitance, however, and this did not occur. Thus no ready explanation can be offered for the fact that morphine has a transient effect on resistance and a prolonged effect on capacitance. It is of interest, however, that Ross and associates in their studies of the digitalis glycosides found that these agents also had only transient effects on resistance vessels but prolonged actions on capacitance vessels.[8]

Most of the information concerning the peripheral vascular effects of morphine has been derived from experimental animals and the varying results of these investigations may be attributed, at least in part, to species differences. The dog was selected for the present studies not only for convenience but also because of the common laboratory animals the dog has physiologic responses to morphine that most closely resemble those of man.[11] The dose response relationship to morphine is quite different in dog and man, however, and in the dog significant effects upon the circulation result only from the intravenous administration of at least 0.5 mg. per kilogram. In many studies doses of 1.0 to 4.0 mg. per kilogram have been utilized and a dose of 75 to 100 mg. per kilogram is described in one as being moderately large. Thus the dose of morphine employed in the present experiments, 0.5 mg. per kilogram, may be considered to be relatively small. When cardiopulmonary bypass was employed, 1.0 mg. per kilogram was given since the drug was diluted by the combined blood volumes of the extracorporeal circuit and the animal.

It would seem to be reasonable to compare the results of the experiments described above to some of the effects of morphine which have been noted in clinical investigations. Drew, Dripps, and Comroe,[1] for example, studied the effects of morphine in both patients and normal subjects and found little change in the blood pressure when the subjects were supine. Many developed hypotension, however, when they were tilted into an upright position and, since this effect could be prevented by the prior application of elastic bandages to the legs, it was concluded that the orthostatic hypotension was due to peripheral pooling of blood. The increases in capacitance recorded in the present experiments not only affirm the validity of this conclusion but indicate that venous pooling is a major pharmacologic effect of morphine which has not been well recognized.

## Summary

The effects of morphine on total peripheral vascular resistance and the capacity of the peripheral vascular compartment were determined in normal dogs. In 13 animals in which systemic flow was maintained constant, morphine (1 mg. per kilogram) caused immediate decreases in resistance averaging 46 ± 20 per cent of the control values. The decrease in resistance was transient and normal or increased resistance was noted 30 minutes after the drug was administered. This effect of morphine on resistance vessels was indirect, however, since no immediate change in pressure occurred when morphine was injected into an isolated perfused vascular bed.

In 13 dogs studied during cardiopulmonary bypass, the capacity of the total peripheral vascular compartment increased after the administration of morphine. Blood volume rose an average of 11 ± 6 ml. per kilogram and systemic

return measured with a flowmeter rapidly decreased after the injection Venous tone determined by major vessel occlusion in 8 dogs decreased from 6 8 ± 1 3 to 3 5 ± 1 1 cm $H_2O$ after morphine (0 5 mg per kilogram) was given The measured changes in both capacitance and venous tone occurred promptly and persisted throughout a 30 minute period of observation

The experiments indicate that increased capacitance and venous pooling are important effects of morphine on the circulation which have not been well recognized

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# Case reports

## Coarctation of the aorta and pregnancy

*Herbert L. Wachtel, Major, MC, USA**
*Stephen W. Czarnecki, Lt. Colonel, MC, USA***
*San Francisco, Calif.*

Aortic rupture and other potentially fatal cardiovascular complications occur in a small but significant percentage of pregnant patients with coarctation of the aorta. Nine patients whose aortic coarctations were resected during pregnancy have been described.[1-4] In 8, the pregnancies were subsequently uncomplicated and terminated with delivery of normal infants. We are reporting an additional case. Since there is no way of predicting which women will develop serious cardiovascular difficulty, and available evidence does not indicate increased surgical risk during pregnancy, we think that resection of the coarctation should be accomplished during the antepartum period.

### Case report

A 20-year-old woman, gravida 1, para 0, was seen initially in the antenatal clinic at Letterman General Hospital on April 17, 1964. She was in her fourteenth week of pregnancy. Since her early childhood she had been troubled with headaches and cold feet, and exercise-induced aching in the triceps surae muscle groups. There was no history suggestive of cardiac decompensation. The patient was unaware of the presence of hypertension or cardiovascular disease.

On physical examination, the blood pressure in both upper extremities was 180/110 mm. Hg. Femoral pulses were markedly diminished and no blood pressure was obtainable in the lower extremities. There were no signs of cardiac failure. Normal sinus rhythm was present. There was no clinical cardiomegaly. The second sound in the pulmonic area was physiologically split. A Grade 3/6 harsh systolic murmur was heard at the base of the heart and could also be heard posteriorly, medial to the left scapula. The electrocardiogram was normal. The chest x-ray film showed notching of the lower margin of the ribs bilaterally. The cardiac silhouette was normal.

A diagnosis of coarctation of the aorta was made and the patient was scheduled for surgical extirpation of the coarctation, which was accomplished during the eighteenth week of pregnancy. A narrow segment of severely coarcted aorta was found immediately distal to the origin of the left subclavian artery. The coarcted segment, together with a small portion of aorta proximal to it, were excised and an end-to-end anastomosis was accomplished. Careful microscopic examination of the specimen revealed no cystic changes in the media.

The postoperative course was uncomplicated and the patient was discharged from the hospital 2 weeks after operation on no medication. Her femoral pulses were normally palpable and she was normotensive. Normal blood pressure persisted during the rest of her pregnancy. On October 12 she went into labor spontaneously and was delivered of a normal female infant weighing 6 pounds and 6 ounces. A mid forceps rotation and delivery were performed. The postpartum course was uncomplicated and she remained normotensive.

### Discussion

It is well established that untreated coarctation of the aorta frequently results in premature death. In the series of Reifenstein and colleagues,[7] 61 per cent of 104

Received for publication Sept. 22, 1965.
*Assistant Chief, Cardiovascular Service, Letterman General Hospital, San Francisco, Calif. Present address: Cardiology Service, William Beaumont General Hospital, Box 423, El Paso, Tex.
**Chief, Cardiovascular Service, Letterman General Hospital; Clinical Professor of Medicine, University of California School of Medicine, San Francisco, Calif.

patients who had survived infancy did not live beyond 40 years of age The four common fatal complications are dissecting aneurysm and rupture of the aorta congestive heart failure bacterial endocarditis and rupture of an intracranial arterial aneurysm

Mendelson [4] in 1960 reviewed the literature and found 200 cases of aortic coarctation associated with pregnancy There were 14 deaths Causes of death were aortic rupture in 8 patients congestive heart failure in 2 patients cerebrovascular accident in 2 patients and bacterial endocarditis in 2 patients Twenty three additional cases have since appeared [1,9,11] with no maternal deaths Thus 14 deaths have been reported in 223 cases a mortality rate of 6 3 per cent

Forty of the 200 patients described by Mendelson[4] had cardiovascular complications during pregnancy an incidence of 21 per cent These complications included heart failure aortic rupture cerebral accident bacterial endocarditis toxemia and dissecting aneurysm of the aorta In a recent report [12] a high incidence of nonfatal cardiovascular renal complications including cardiac decompensation pedal edema dyspnea hypertension and albuminuria were noted These complications were present in 16 of 32 pregnancies In contrast 19 of 21 pregnancies occurring after resection of the coarctation were free of cardiovascular renal problems

There appears to be an increased incidence of dissection and rupture of the aorta in pregnancy regardless of the presence of coarctation In the series of Schnitker and Bayer [13] 24 (48 per cent) of 49 women under 40 years of age who sustained aortic dissection were pregnant In another series[14] consisting of 70 females under 40 years of age who sustained aortic dissection 36 (51 per cent) were pregnant Of 25 women with aortic dissection reported by Hirst and co-workers [15] 12 (48 per cent) were pregnant Thus a double predisposition to aortic dissection and rupture is present in pregnant women with coarctation of the aorta

The increased incidence of aortic dissection in the two situations may have a common anatomic basis In the series of Hamilton and Abbott [16] the aortas of 13 patients with coarctation who died of dissection and rupture were examined histologically In 12 cases marked changes in the media were seen with interruption and diminution of the elastica and hyaline and fatty degeneration Hirst and colleagues[15] described similar changes in each of 7 patients who died of dissection and rupture They also reported histologic studies in 7 patients who died during pregnancy of causes other than aortic dissection Accumulations of mucoid material in the aortic media most prominent in the ascending aorta and the arch were found in 6 patients Similar abnormalities in pregnant patients with aortic coarctation who die of aortic rupture have been noted by other workers [17,18] The pathogenesis of these medial lesions is not well understood

Mendelson [4] in a review of the literature found 51 cases in which the coarctation had been resected prior to pregnancy There was no maternal death during pregnancy in these patients Mortensen and Ellsworth[1] described 8 patients who conceived after their coarctations had been resected There were 21 pregnancies with no maternal mortality On the other hand Jordan[19] reported the case of a woman who sustained an aortic dissection with rupture during pregnancy 6 years after surgical correction of her aortic coarctation The dissection occurred in the ascending aorta the site of operative anastomosis was undisturbed Thus one maternal death has been described in 60 patients a mortality rate of 1 7 per cent which is significantly lower than the 6 3 per cent mortality when pregnancy and coarctation are present without correction of the latter

Mendelson [20] in 1940 suggested that therapeutic abortion and sterilization were indicated in patients with aortic coarctation who became pregnant As more cases were reported it became obvious that the prognosis was not so grave as had been suspected This knowledge coupled with the advent of corrective surgery resulted in a more conservative approach In 1955 Rosenthal [1] recommended resection of the coarctation if the pregnancy was less than 20 weeks in duration If the diagnosis was made in the latter half of pregnancy he recommended close observation with surgical correction several weeks after delivery In more recent years several work

ers[8,11,12] have advised no surgical therapy during pregnancy regardless of its duration at the time the coarctation was discovered Mendelson[8,2] thinks that the pendulum has swung excessively toward the conservative approach In his opinion the relatively high morbidity and mortality rates in coarctation associated with pregnancy justify correction of the coarctation during the antepartum period

The mortality rate in resectional surgery for aortic coarctation is low Schuster and Gross[4] reported a mortality rate of 4 1 per cent in 487 operations They stated that in the absence of extremes of age and other cardiovascular abnormalities patients with coarctation could be operated upon with a risk of less than 2 per cent At Letterman General Hospital 13 cases of post-ductal coarctation have been surgically corrected since 1960 There has been no mortality Resection is advised on diagnosis in most cases

Ten patients including the one reported on here in whom resection of the coarctation was accomplished during pregnancy have been described[1-4] Nine patients had subsequently normal pregnancies with delivery of normal infants In Eastman's patient[4] in whom surgery was performed during the first month of pregnancy an aneurysm developed at the anastomotic site and ruptured during the seventh antepartum month resulting in death of mother and fetus Whether gestational factors contributed to the appearance of the aneurysm is of course unknown

The cases that have been described do not suggest increased surgical risk during pregnancy There is no evidence that aortic surgery has a deleterious effect on the fetus The mortality rate from cardiovascular complications in pregnant patients with aortic coarctation is 6 3 per cent the morbidity rate is 21 per cent Since it is not possible to predict which women will develop serious cardiovascular difficulty we think that resection of the coarctation should be accomplished during pregnancy

## Summary

A case of coarctation of the aorta in a pregnant patient is reported The coarctation was surgically corrected during the eighteenth week of pregnancy with a subsequently uncomplicated pregnancy and delivery This is the tenth patient described in whom resection of the coarctation was accomplished during pregnancy The subject of coarctation of the aorta associated with pregnancy is reviewed The incidence of cardiovascular complications is about 20 per cent Since there is no way of predicting which patients will develop cardiovascular difficulty we think that surgical correction of the coarctation should be accomplished during the antepartum period

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# Constrictive pericarditis associated with hemangioma of the pericardium

*Charles Wender, M.D.**
*Joseph E. Acker, Jr., M.D.*
*Atlanta, Ga.*

The low incidence of primary pericardial tumors has been acknowledged. The rare involvement of the pericardium by an endothelial tumor has been reviewed by Hicken.[1] He collected from the world literature 12 cases of isolated hemangiomas involving the pericardium. He included his own case of 36-year-old man who had multiple hemangiomas of the visceral and parietal portions of the pericardium with associated hemopericardium and eventual death.

This paper is the second report of multiple hemangiomas involving the pericardium, but the case is unique because of two features: (1) multiple involvement of the pleura, thymus, and pericardium and (2) pericardial constriction.

## Case report

G. F., a 16-year-old white girl, was admitted to the University of Tennessee Memorial Research Center and Hospital on Oct. 31, 1963, with a productive cough that had been present for 10 months and that previously had been treated as bronchitis and pneumonia. Findings at hospitalization elsewhere on May 5, 1963, were marked cardiomegaly and pulmonary congestion. Treatment with digitalis, steroids, and antibiotics resulted in little improvement. Hepatosplenomegaly, tachycardia, and intermittent pedal edema were later noted and responded temporarily to mercurial diuretics. Progressive deterioration occurred in spite of bed rest and intensive treatment.

Examination at the time of admission revealed an extremely dyspneic, pale, chronically ill white girl with cyanosis. The blood pressure was 176/80 mm. Hg. Pertinent findings were: venous distention, diffuse moist râles, expiratory wheeze, cardiomegaly without murmurs, liver enlarged 10 cm. below the right costal margin, splenomegaly, pitting pretibial edema, no clubbing of the fingers, and no pericardial rub or knock.

The findings were normal for all of the following: complete blood count, Venereal Disease Research Laboratory test, sheep red blood cell agglutination titer, L.E. preparations, bleeding and clotting times, blood urea nitrogen, serum electrolytes, SGOT, SLDH, sputum, urine and blood cultures, histoplasma complement fixing antibodies, and tuberculosis, blastomycosis, and coccidioidomycosis skin tests. Histoplasma skin test was positive. The corrected Wintrobe sedimentation test was 21 mm. in 1 hour, and urinalyses included 10 to 12 leukocytes and 8 to 10 erythrocytes per high power field. The antistreptolysin-O titer was 333 Todd units. Prothrombin time was 18.1 seconds with a control of 13 seconds. Serum protein electrophoresis showed a total protein of 6.37 and albumin of 2.4 Gm. per 100 c.c. Low voltage, sinus tachycardia, and S-T changes due to digitalis were noted on serial electrocardiograms. Severe pulmonary congestion and cardiomegaly were seen on x-ray films. The venous pressure was 180 mm. of saline, rising to 230 mm. with pressure in the right upper quadrant. The arm-to-tongue Decholin circulation time was 12 seconds.

Treatment with bed rest, sodium restriction, digitalis, and mercurial diuretics resulted in a loss of weight from 112 to 101 pounds, but dyspnea, fine pulmonary râles, and hepatomegaly persisted. The pressure (mm. Hg) revealed by right heart

From the University of Tennessee Memorial Research Center and Hospital, Knoxville, Tenn.
Received for publication Sept. 30, 1964.
*Address: Emory University Clinic, Department of Internal Medicine, Atlanta, Ga., 30322.



Fig. 1. A section from the pericardium show the capillary and cavernous appearance of the hemangioma. The exten e fibrous reaction i evident.



Fig. An add tional section from the pleura show a sim lar involvement.

catheterization were right atrium 34/19 right entricle 42/70 pulmonary artery 40/27 and mean pulmonary capillary 24.

A diagnosis of constrictive pericarditis of un determined etiology was made and surgery was undertaken on Nov. 12 1963. A median sternotomy was performed and at once a large uperior med a tinal mass thought to be thymu was noted.

Multiple small vascular lesions were seen in the pericardium isceral pleura and parietal pleura. Frozen sections were studied and were reported to show hemangiomata of the th mus pleura and pericardium. The pericardium was markedly thick ened and constricted both entricles however it was removed with relative ease. Immediately after pericardiect my the enous pressure fell from 250

to 80 mm of saline. Despite clinical improvement, tachypnea and dyspnea persisted. Digitalis and oral diuretics were continued after the patient was discharged on Dec. 14, 1963.

The final pathologic interpretation was cavernous and capillary endothelial structures with intense fibroblastic proliferation.

On Jan. 1, 1964, she was readmitted to the hospital with marked dyspnea and orthopnea. The blood pressure was 176/70 mm. Hg with no pulsus paradoxus noted. Other findings were: heart rate 140, respirations 37, temperature 98.4 F., symmetrical distention of the neck veins, lower costal bulging and flatness to percussion with absent breath sounds in both lung bases, medium rales over upper lung fields, cardiomegaly with no murmur or rub, hepatomegaly 10 cm. below the right costal margin but no splenomegaly. On the chest x-ray film, bilateral hazy densities due to pleural effusion were noted. The hematocrit was 29 volumes per cent. Five hundred cubic centimeters of dark red fluid was obtained on thoracentesis on the right side. The hematocrit of this fluid was 17 volumes per cent. Repeated bilateral thoracenteses of serosanguineous fluid resulted each time in temporary improvement.

The pressures (mm. Hg) revealed by another right heart catheterization were: right atrium mean 6, right ventricle 35/8, pulmonary artery 35/17, and mean pulmonary capillary 10.

After repeated blood transfusion, a left thoracotomy with pleurectomy was performed on Feb. 7, 1964, after which 10 c.c. of nitrogen mustard was instilled into the pleural space to cause adherence of the visceral pleura to the chest wall. Eighteen days later, the same procedure was applied to the right pleural space. The hematocrit stabilized and the heart rate slowed before the patient was discharged from the hospital on March 4, 1964.

## Discussion

The associated involvement of multiple intrathoracic structures has not been a feature of other reports of pericardial hemangiomas, nor has pericardial constriction been recorded as an associated finding. Puder and Daniel in 1932 first suggested that hemorrhage into the pericardium might be followed by pericardial constriction. Laszlo[1] reported the necessity of pericardiectomy to relieve pericardial constriction 11 months after an acute myocardial infarction with hemopericardium secondary to therapy with bishydroxycoumarin.

Pericardiectomy was also necessary for pericardial constriction in Segal and Tabatznik's cases[4] of penetrating stab wounds of the chest, in McKusick's case[5] after a blunt injury, and in Goodkind and associates' cases[6] after blunt nonpenetrating chest trauma.

Wilson and associates in 1962 studied the absorption of blood from the pericardial space with the use of Cr 51 labeled red blood cells. This work had been preceded by previous studies of the absorption of blood from the pleural space.[8]

Their data confirmed a slower and less complete recovery of blood from the pericardial cavity than from the pleural space. Autopsy failed to reveal significant pericardial changes, whereas some pleural edema resulted from the injection of blood into the pleural space.

Ehrenhaft and Taber[9] pursued the significance of intrapericardial hemorrhage and resultant constriction of the pericardium by injecting autogenous blood and the lipid fraction from this blood into two separate groups of dogs. The pericardial reaction was slight in both groups. However, one dog which received the intrapericardial lipid fraction developed extensive fibrosis. This study employed only one injection rather than repeated injections of blood or lipid fraction into the pericardium.

The preceding clinical reports and studies do not afford adequate grounds on which to base an opinion about the importance of intrapericardial hemorrhage in the pathogenesis of constrictive pericarditis. Most previously reported pericardial hemangiomas have been asymptomatic and were incidental findings at autopsy. Pericardial tamponade or gross pericardial constriction by the mass of the tumor itself has been the primary feature in symptomatic individuals. The intense pericardial constriction in our case was not the result of the tumor mass itself. The microscopic feature of the pericardium was characterized by an extensive fibrous reaction. The etiology of this fibrous reaction is not clear. However, the nature of the tumor and clinical documentation of repeated episodes of intrapleural hemorrhage make it reasonable to assume that repeated episodes of intrapericardial hemorrhage occurred.

## Summary

This represents the second case of multiple hemangiomas involving the pericardium reported in the literature.

The association of intrapericardial hemorrhage with pericardial constriction has been reviewed. Further investigative work

seems to be necessary to clarify their relationship.

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# Double-outlet right ventricle with pulmonary valve atresia

## Report on a patient surviving to age 25

*J. H. Rogoff, M.D.**
*Wm. Anthony, M.D.***
*Cleveland, Ohio*

This report describes the case of a 25 year old Puerto Rican woman who was found to have both great vessels arising from the right ventricle associated with two small ventricular septal defects, pulmonary infundibular stenosis, and pulmonary valve atresia.

The origin of both aorta and pulmonary artery completely from the right ventricle has been uncommon but has been diagnosed more frequently in the past few years. In order to be compatible with life it must be associated with one or more ventricular septal defects. In addition, half of the cases are associated with pulmonary infundibular and valvular stenosis. However, to the best of our knowledge this is the first case report of a patient living to the age of 25 years with the lesion associated with pulmonary valve atresia.

The abnormality, also known as "double-outlet right ventricle," was first described by Peacock[1] in 1866. Spitzer[2] in 1923 considered the malformation to be a type of transposition of the great vessels and proposed a phylogenetic theory to account for its development. Maude Abbott[3] in a review of 1,000 congenital cardiac defects recorded 2 cases in 1936. Additional cases found at autopsy have been recorded by Astley[4] in 1952 and by MacMahon[5] in 1953. In 1957 the first clinical classification was provided by Witham,[6] who presented 4 cases and referred to 3 others. Two of these cases were classified as the "Eisenmenger type," in that no pulmonary stenosis was present, and 2 others, in which pulmonary stenosis was present, were classified as the "Fallot type." One of the latter was that of a 2.64 kilogram newborn infant who failed to breathe and was pronounced dead an hour after birth; postmortem examination revealed pulmonary valve atresia, a five-leaflet common atrioventricular valve, and an absent atrial septum.

Neufeld[7] in 1961 described the cases of 13 patients in whom both great vessels arose from the right ventricle, with pulmonary stenosis in 5 of them. Eighteen cases without associated pulmonary stenosis were presented by Engle[8] in 1963; 10 of these cases were diagnosed at autopsy and 8 were diagnosed during life by angiography. Mirowski[9] in 1963 presented a series of 22 cases of double-outlet

From the Departments of Medicine and Surgery, Western Reserve University, Cleveland Metropolitan General Hospital, Cleveland, Ohio.

Received for publication [illegible]

*Michael Reese Hospital, Chicago, Ill. Address: Apt. 1112, 2901 South Parkway, Chicago, Ill. 60616.
**Captain, USAF, [illegible] AFB, San Antonio, Tex.

right ventricle and pulmonary stenosis collected from 1946 to 1963. Of these, 12 were diagnosed at autopsy or at surgery, whereas 10 were diagnosed during life by angiography.

The circulatory abnormality associated with both great vessels arising from the right ventricle depends upon the presence or absence of pulmonary stenosis. If no stenosis exists, there is usually no cyanosis and the patients are, according to Engle,[3] clinically very similar to those with a ventricular septal defect and pulmonary hypertension. The chief manifestations are easy fatigability and dyspnea on exertion. If pulmonary stenosis is present, the patients are almost always cyanotic and have a clinical course similar to that of patients with the tetralogy of Fallot complex, as observed by Astley.[4] These patients, in addition to easy fatigability and dyspnea on exertion, are polycythemic.

Thus, the diagnosis of common origin of the great vessels from the right ventricle cannot be made from the clinical history and physical examination alone. Rather, the diagnosis is suggested by electrocardiographic findings and data from cardiac catheterization. It is confirmed by angiocardiography, preferably cineangiocardiography. Several authors emphasize the point that this lesion is not usually evident from external inspection of the heart at the time of surgery, since the lesion is intracardiac and the great vessels externally may seem to be in their normal relationship. Engle[3] reports the cases of 2 patients who were thought preoperatively to have simple ventricular septal defect but who died shortly after these defects were repaired. Only at autopsy was it found that the aorta arose from the right ventricle. Accurate preoperative diagnosis is thus essential to the successful treatment of this lesion.

Mirowski[5] in a report of 22 cases noted several points that distinguish these patients from those with the tetralogy of Fallot. Left ventricular hypertrophy was seen in 75 per cent of these patients, whereas this condition is virtually unknown in uncomplicated tetralogy of Fallot. 63 per cent had complete right bundle branch block, which is very unusual in the tetralogy of Fallot. In 60 per cent of Mirowski's reported cases the patients had first degree heart block, and in 80 per cent the P-R interval was greater than 0.88 second (normal, 0.75 to 0.09 second), an extremely rare occurrence in patients with the tetralogy of Fallot. Right ventricular hypertrophy, present in both lesions, tends to be greater when both great vessels arise from the right ventricle.

The findings at cardiac catheterization depend upon the presence or absence of pulmonary stenosis, but in either case the important finding is that the pressure in the right ventricle is equal to, or almost equal to, the systemic pressure. Engle states that "patients with ventricular septal defect and right ventricular pressure near systemic should be suspected of having aortic transposition."

Confirmation of the diagnosis preoperatively can usually be accomplished with cineangiocardiography. On the lateral views the aorta is displaced *anteriorly* above the right ventricle and anterior to the ventricular septum. Both great vessels opacify at the same time, depending on the degree of pulmonary stenosis and on whether the pulmonary artery is in its normal position. The other important differential finding is that both semilunar valves are in the same coronal and cross-sectional body planes.

Surgical therapy for this lesion has consisted of (1) Blalock-Taussig anastomosis, (2) creation of an atrial septal defect, (3) relief of pulmonary stenosis if present, and (4) intracardiac surgical correction using a Teflon conduit graft. Taussig[10] makes the point that the first of these procedures may be unsatisfactory in any given case because of the danger of subsequent congestive heart failure.

There have been several reports of surgical correction of this lesion. The first, performed by Lillehei and reported by Lucas[11] in 1961, was in a 19-year-old male who had no pulmonary stenosis. A Teflon patch was sutured to the lower and lateral borders of the ventricular septal defect and then to the root of the aorta in the right ventricle, thereby partitioning the right ventricle from the left, forming a "conduit" for the blood from the left ventricle to the aorta. This patient died several days after the operation of acute massive

necrosis of the liver which was thought to have been due to inadvertent kinking of the inferior vena cava during the operation

McGoon[1] in 1961 reported a similar operation in a 7 year-old girl again without pulmonary stenosis. Levy[13] reported the first successful case of correction in a 7 year old girl with associated pulmonary infundibular stenosis and aortic insufficiency. The infundibulum was resected and a conduit prosthesis was inserted from the ventricular septal defect to the root of aorta. The patient left the hospital 2 weeks after the operation. Redo[14] in 1963 reported the case of a 10-year old girl without pulmonary stenosis who successfully underwent the insertion of a conduit fabric prosthesis

## Case report

*History* A 25 year-old single unemployed Puerto Rican woman was referred to Cleveland Metropolitan General Hospital from Rio Piedras Municipal Hospital Puerto Rico because of cyanotic congenital heart disease

The patient who had been a very small infant had been cyanotic from birth. From the age of 1 year she had tired easily on any kind of exertion. Her growth and mental development had otherwise been normal but she had left school in the third grade because she could not keep up physically with the other children

At the age of 19 years she had had a single episode of syncope on arising from a chair and she had been confined to bed for 6 months. During this time she had developed painful swollen knees. She also had had a single bout of hemoptysis. Right heart catheterization had been attempted but was unsuccessful. She had required phlebotomy a total of seven times in 7 months. At the age of 22 she was [illegible]

One year prior to admission to this hospital the patient had begun to experience a burning precordial pain on exertion. On the morning of the day of admission she had a bout of syncope

The *family history* was of interest in that the patient's mother had died of diabetes 3 months previously. Three older sisters were living and well

*Physical examination* Examination revealed a well nourished but thin woman who had a temperature of 3[illegible] 4 C pulse 104 and regular respiration 16. The blood pressure was 130 systolic and 90 diastolic mm Hg. Body weight was 44 8 kilos and height was 147 3 cm. The lips mucous membranes [illegible] nail beds were cyanotic. There were active carotid pulsations with a prominent diffuse cardiac apical thrust. There was increased activity over the right ventricular outflow tract but no thrill was palpable. The heart was not clinically enlarged. On auscultation there were two distinct systolic clicks and Grade 3/6 harsh holosystolic murmur beginning in mid systole and ending with a sharp accentuated single second sound heard in the second and third left intercostal spaces. A few fine dry crackling end inspiratory râles were heard over the base of the left lung. The patient had no peripheral edema but showed marked hypertrophic pulmonary osteoarthropathy. All of the joints of the extremities were hyperextensible. The knees were swollen and tender to deep palpation. The neurological examination was negative

Because of an infiltrate in the left upper lung lobe seen on the chest film (Fig 1) she was admitted to the tuberculosis ward

*Laboratory examination* Urinalysis revealed a specific gravity of 1 015 a trace of protein and no sugar or acetone. The urinary sediment was negative. The hematocrit was 59 per cent the hemoglobin 16 8 Gm per 100 ml the white cell count was 9 164 with 54 per cent neutrophils 33 per cent lymphocytes 12 per cent monocytes and 1 per cent basophil. Blood chemistry and liver function tests were within normal limits. A second strength tuberculin skin test showed 14 mm of erythema and induration in 48 hours and the histoplasmin skin test showed 40 mm of erythema and induration in 48 hours. Repeated throat cultures were negative. Three gastric aspirates were negative for acid fast bacilli. A stool examination for ova and parasites revealed only a few Trichuris ova. An electrocardiogram revealed only right ventricular hypertrophy and strain and sinus tachycardia (Fig 2)

*Catheterization* The data obtained at right heart catheterization and in the pulmonary function laboratory are recorded in Tables I and II. The indicator-dilution curve with injection into the right atrium and withdrawal from the right brachial artery was consistent with a large right-to-left shunt. A subsequent unsuccessful attempt at car



Fig 1 Roentgenogram of the chest taken at the time of admission shows the lesion in the left upper lobe (arrow)

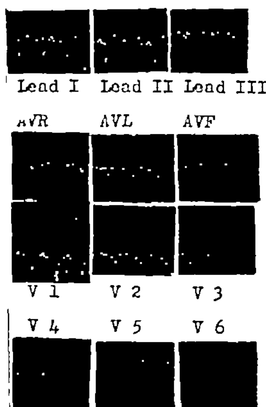



Fig. 2. Electrocardiogram taken at the time of admission shows right ventricular hypertrophy and strain with sinus tachycardia.



Fig. 3. Roentgenogram of the chest taken during attempted right heart catheterization reveals that the lesion in the left upper lung lobe is extensive bronchial circulation (confirmed at autopsy). Catheter in azygos vein; film taken 6 seconds after injection of 40 c.c. of contrast material.

diac catheterization revealed that the catheter was in the azygos system and that the lesion in the left upper lung lobe opacified with the azygos vein on angiocardiography, suggesting an extensive bronchial circulation (Fig. 3).

*Fluoroscopy.* Fluoroscopy revealed that the vascular markings in the lungs were decreased bilaterally. The heart was slightly enlarged, with the right ventricle being the only chamber showing enlargement. The pulmonary artery segment and aortic arch both appeared to be diminished in size. A barium swallow was negative. Cineangiocardiography was thought to reveal extremely poor opacification of the pulmonary artery, with the major portion of the contrast material passing out through the aorta. A markedly narrowed outflow tract of the right ventricle was also thought to be demonstrated. In retrospect, it was seen that the aorta was anterior to the ventricular septum on the lateral views.

*Operation.* On the ninety-fourth hospital day the patient underwent a Blalock-Taussig anastomosis of the right subclavian artery to the right main branch of the pulmonary artery, using an interposed free vein graft obtained from the right saphenous system.

The right main branch of the pulmonary artery was approximately 5 mm. in diameter.

The patient did well for the first 36 hours after operation. She was alert and appeared to be less cyanotic. The peripheral arterial oxygen saturation rose from 60 per cent preoperatively to 72 per cent the day after the operation. However, on the third postoperative day the patient had two anoxic spells, lost consciousness, and gradually became unresponsive. Despite vigorous supportive measures she died on the fifth postoperative day.

*Autopsy.* Autopsy revealed that the Blalock-Taussig anastomosis was patent. Gross inspection of the heart revealed that the aorta arose from the heart more anteriorly than usual. The pulmonary artery and its branches and the aorta and its branches were normal except that the bronchial arteries were greatly enlarged.

Dissection of the heart (Fig. 4) showed that the venae cavae, the right atrium, and the tricuspid valve were normal. The right ventricular wall was greatly hypertrophied. The pulmonary artery arose in its usual position although there was marked stenosis of the pulmonary outflow tract by a large muscle mass. The pulmonary valve was cone shaped, fibrous, and atretic. The aorta arose from the right ventricle to the right of and slightly anterior to the pulmonary artery. The coronary artery ostia and the aortic valve were normal. There were two ventricular septal defects, each about 1 cm. in diameter. The upper one was below and to the right of the aortic valve, separated from it by the crista supraventricularis, which was divided by the defect into two branches, one cephalad and one caudad to the defect. The lower septal defect was low in the muscular portion of the septum, approximately 3 cm. below the aortic valve. The left atrium and mitral valve were normal. The left ventricular wall was markedly hypertrophic. The only left ventricular outlets were the ventricular septal

*Table I Cardiac catheterization*

| Pressures (mm Hg) | | | Oxygenation | | |
|---|---|---|---|---|---|
| | | | Oxygen | Volumes per cent | Saturation (%) |
| Right atrium | 8 mm | Maximum | Arterial capacity | 2[illegible] 10 | |
| | 2 mm | Minimum | Superior vena cava | 11 14 | 50 5 |
| Right ventricle | 128 mm | Systolic | High right atrium | 11 58 | 52 3 |
| | 6 mm | End-diastolic | Low right atrium | 11 94 | 54 1 |
| Brachial artery | 134 mm | Systolic | Low right ventricle | 17 16 | 77 6 |
| | 92 mm | Diastolic | Mid right ventricle | 11 67 | 52 6 |
| | 105 mm | Mean | Brachial artery | 13 98 | 63 2 |

*Table II Pulmonary function*

| | Performance | Comparisons |
|---|---|---|
| One-second vital capacity | 2 37 liters | 75 per cent total vital capacity |
| Two-second vital capacity | 3 10 liters | 98 7 per cent total vital capacity |
| Total vital capacity | 3 14 liters | 120 per cent Normal |
| Total expiration time | 3 5 seconds | |
| Maximum breathing capacity | 70 liters/min | Predicted 117 liters/min |
| Walking ventilation rate | 15 7 L/M²/min | Normal 7–11 L/M²/min |
| Dyspnea index (walking ventilation/MBC) | 0 23 | Predicted 0 06–0 10 |

According to predicted value based on body surface calculated from weight and height using the DuBois formula.



Fig. 4 Heart at postmortem shows hypertrophied right ventricle with aortic valve and two ventricular septal defects (arrows).

defects. The atrial septum was intact and the ductus arteriosus was closed.

## Discussion

This 25-year-old woman was thought preoperatively to have a tetralogy of Fallot complex. Her preoperative work-up strongly suggested the tetralogy, whereas many of the criteria for making the diagnosis of "double-outlet right ventricle" as discussed above were unfulfilled. Nevertheless, the right ventricular pressure was approximately equal to systemic pressure, and a review of the cineangiocardiography after autopsy disclosed that the aorta did indeed arise anterior to the ventricular septum. Although systemic-pulmonary artery anastomosis seemed to help this patient clinically for a short time, it did not prevent the recurrence of anoxic episodes. The fact that there were two small ventricular septal defects, one of which was located some distance from the aortic root, would most likely have precluded the insertion of a conduit type of "graft." Possibly, the lower septal defect could have been closed and a conduit inserted between the upper defect and the aortic root. This would have had to be accompanied by widening of the pulmonary outflow tract and a pulmonary valvulotomy. Whether this would have allowed sufficient outflow for the left ventricle is a moot question because of the small size of the septal defect.

## Summary

The case of a 25-year-old woman who had both great vessels arising from the right ventricle, two ventricular septal defects, pulmonary infundibular stenosis, and pulmonary valve atresia has been presented, with a brief review of pertinent literature. Unusual features of this case included right ventricular hypertrophy pattern in the electrocardiogram and bronchial collateral circulation to the left lung that was thought radiographically to be tuberculosis.

We would like to express our appreciation for the invaluable aid of Dr. John H. Kennedy, Department of Surgery, and Dr. Salvatore Sancetta, Department of Medicine of the Cleveland Metropolitan General Hospital. We are also grateful to Dr. F. Simeone, who read and corrected the manuscript. The achievements of this paper are largely theirs; the faults are ours.

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# Clinical pathologic conference

*Madison S. Spach, M.D.**
*Arthur M. Martin, M.D.*
*James B. Sidbury, Jr., M.D.*
*Donald B. Hackel, M.D.*
*Ramon V. Canent, Jr., M.D.*
*Durham, N. C.*

### Clinical abstract

This white male infant was first seen at Duke Hospital when he was 4½ months old. During the first 3 months of life he had been constipated, and it was noted that his muscles were quite firm and hard. Increased vomiting was noted during the third month of life, and for 2 weeks prior to admission he had had episodes of crying during his feedings. His cry became weaker, and prominent neck veins were observed by the parents. At birth, the umbilical cord and placenta of the patient had been sent to Dr. Sidbury for analysis, and alpha glucosidase was found to be absent. The past history revealed that he was the product of an uncomplicated pregnancy. A brother who died at the age of 8 months was known to have had Type II glycogenosis.

Physical examination revealed that the patient maintained a frog-like position (Fig. 1). He appeared to be mildly cyanotic and was in moderate respiratory distress. He weighed 5.5 kilograms, the pulse rate was 140 beats per minute and regular. Respirations were rapid, with intercostal and substernal retractions. The left side of the chest was more prominent than the right, with dullness to percussion over the entire left chest. Rales were present over the left chest posteriorly. The femoral arterial pulses were normal, the neck veins were distended, and by palpation the heart seemed to fill the whole left chest. There was a Grade 2/3 apical harsh systolic murmur with a prominent third sound. The liver was palpable 6 cm. below the right costal margin. The tongue was prominent. The muscles did not feel prominent or firm. No deep tendon reflexes were obtainable, and there seemed to be generalized hypotonia.

The electrocardiogram (Fig. 2) revealed a P-R interval of 0.08 second with left ventricular hypertrophy evidenced by ab[illegible] small, deep Q and a tall R wave in Lead $V_6$. Additionally, the Q wave was abnormally deep in Lead I. The T vector was abnormally positioned to the left at approximately −15 degrees.

Laboratory studies of the blood gave normal results. Urinalysis showed 2+ proteinuria and no glycosuria.

The patient was acutely ill on admission. Despite oxygen and moisture therapy, there was persistence of the cyanosis. The heart murmur became louder, labored respiration continued, and the neck veins became more distended. Penicillin and streptomycin therapy was started. His condition worsened, and 12 hours after admission he suddenly sat up, gagged, and ceased breathing. Attempts at resuscitation were unsuccessful.

### Discussion

DR. SPACH: This case concerns an infant with a classic history of Type II glycogen storage disease (Pompe disease).[1] The clinical history of gastrointestinal tract difficulty (vomiting early, followed by constipation), weak muscles, enlarged tongue, and typical frog-like position exhibited by the patient on admission are all classic manifestations of Type II glycogenosis with accumulation of glycogen in excessive amounts in all tissues, especially in the heart. This condition comes under the category of several primary endomyocardial diseases as discussed by Lambert and Vlad[2] with the development of heart failure during the first year of life, massive cardiomegaly, absence of central shunts, and

*From the Departments of Pediatrics and Pathology, Duke University Medical Center, Durham, N. C.
This study was supported by United States Public Health Service Grants HTS-5 [illegible] and AM [illegible].
Received for publication Jan. 24, 1966.
Address: Department of Pediatrics, Duke University Medical Center, Durham, N. C. 27706.



Fig. 1 Typical frog like position exhibited by patient. The position is typical of infants with Type II glycogenosis

absence of significant cardiac murmurs. This group of diseases includes anomalous origin of the left coronary artery from the pulmonary artery, endocardial fibroelastosis, myocarditis, cardiac enlargement of unknown cause, and Type II glycogenosis. Clinicians are encountering with increasing frequency many of the above mentioned conditions with presumed superimposed (secondary) endocardial fibroelastosis with the common denominator being that of an enlarged left ventricle. The apical systolic murmur in this patient becomes quite significant in this regard. Did this patient have mitral insufficiency with possible superimposed endocardial fibroelastosis or could the murmur have been related to obstruction of the left ventricular outflow tract due to massive septal hypertrophy? Ehlers and co-workers[4] have documented in this disease the occurrence of left ventricular outflow obstruction secondary to the massive hypertrophy of the left ventricle with bulging of the septum into the outflow tract. In this situation the clinician is presented with quite a dilemma in the face of the congestive heart failure since treatment with digitalis may increase the strength of left ventricular contraction with subsequent greater tightening of the muscular subaortic ring as suggested by Hohn and associates.[5] Thus in this disease when outflow obstruction occurs the use of digitalis may be more harmful than helpful although actual documentation of such an effect of digitalis in Pompe's disease remains to be confirmed.

The electrocardiogram is of considerable aid in distinguishing this disease from other types of primary endomyocardiopathies. Anomalous left coronary artery leads to myocardial infarction and in symptomatic patients there are the typical findings of an anterolateral myocardial infarct. Myocarditis and endocardial fibroelastosis do not exhibit the prominent Q waves in Leads I and $V_6$ as characteristically present

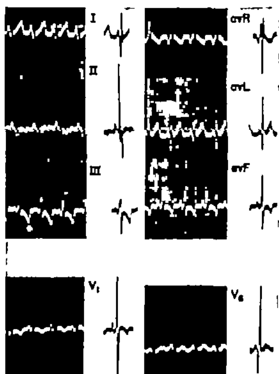



Fig. 2 Electrocardiogram obtained on admission. Note the deep Q waves in Leads I and $V_6$, the short P-R interval (0.08 second), and the abnormal T waves.

in Pompe's disease (Fig. 2).* Also this patient demonstrated the characteristic shortening of the P-R interval so commonly present in this condition.

Currently, the classic clinical features and familial aspects of this condition are so well known that an accurate diagnosis has become much less of a problem than it was a decade ago. Possibly Dr. Sidbury will comment on the value of determinations of alpha glucosidase in the cord and placenta of the newborn as an aid to earlier diagnosis. To date, therapeutic measures have merely been supportive and have not significantly altered the course of the disease. Treatment of associated respiratory infections, especially pneumonia secondary to obstruction of the left bronchus as probably occurred in this patient, may help slightly. In 3 patients whom we have seen with Dr. Sidbury, the terminal days of life were characterized by severe pulmonary infection with augmentation of congestive heart failure.

Thus, although we can diagnose this condition with little difficulty at the present time, we are at a complete impasse to know what to do about improving cardiac function to allow survival even past a year. That this is a progressive disease, there can be little question. X-ray films and electrocardiograms in the newborn period are usually normal, and most patients become symptomatic by 6 months of age. Possibly, our pathologists and metabolic investigators can suggest hopeful avenues for research to improve therapy.

DR. MARTIN: Although various questions have been raised by the clinician, one fact is quite certain. This child did have glycogen storage disease, Type II. Various names have been used to identify this disease. The one which best fits this condition is "generalized glycogenosis." It is not a disease limited to the myocardium. In fact, some of the most striking pathologic changes are found elsewhere. From a functional point of view, the cardiac changes are more prominent.

The heart in this case was markedly enlarged, weighing 150 grams (normal for this age is 27 to 29 grams). All chambers were dilated and hypertrophied. The right ventricular wall was 4 mm. thick, and the left ventricular wall measured 1.2 cm. The foramen ovale was anatomically patent but I do not think that this contributed to the cardiac impairment. The endocardial surface of the left ventricle was opaque and thickened (endocardial fibroelastosis), especially that overlying the base of the interventricular septum. When endocardial fibrosis is present in glycogen storage disease, it is more prominent in hearts of older infants than in the newborn. There was no evidence of obstruction of the left ventricular outflow tract. The mitral valve was mildly involved by the endocardial fibroelastotic changes, and it is possible that mitral insufficiency may have accounted for the prominent apical murmur noted by the clinicians.

Cardiac enlargement such as this must be considered to be a space-occupying lesion. Grossly, the heart was seen to occupy almost the entire left chest. The left lung was compressed posteriorly and was almost totally atelectatic—only the very tips of the apex and base were crepitant. The left main stem bronchus was flattened by the enlarged heart, having only a slit-like orifice. Microscopically, this lung showed marked atelectasis.

The right lung was quite different. Grossly, it appeared to be normally crepitant, but microscopically there were widespread areas of bronchopneumonia, chronic congestion, and pulmonary edema. In addition, the right bronchus and segmental bronchi as well as the trachea and pharynx were filled with vomitus. The stomach was markedly distended with similar material. The material did not enter the left bronchus because of its compression by the heart. This aspiration of vomitus probably occurred as an agonal event. It must be emphasized that in addition to the obvious cardiac problems in this case, this patient had marked respiratory impairment.

Microscopically, the myocardium showed the typical "lacework" pattern in longitudinal section and a "honeycombed" appearance in cross section (Fig. 3). There was marked vacuolar formation in the central portions of the myofiber, especially about the nuclei. The nuclei, however, appeared to be essentially normal. Stains for glycogen showed diffuse deposits within the vacuoles, as well as the fibrillar portions of these cells. These changes in the myofibers

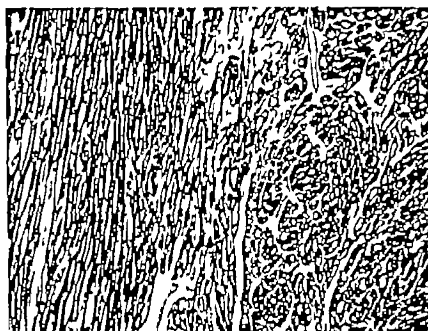


Fig 3 Typical histologic section of myocardium in generalized glycogenosis There is the prominent lacework pattern in longitudinal section and honeycombed pattern in cross sections Hematoxylin and eosin ×120

were present throughout the myocardium

The liver also was enlarged light yellow and soft and weighed 265 grams Microscopically the liver contained much stainable glycogen but otherwise appeared to be within normal limits Recent work by Baudhuin Hers and Loeb[7] has shown that much of this hepatic glycogen is found within membrane lined vacuoles which they refer to as lysosomes Structurally this glycogen appears to be the same as that found elsewhere in the cytoplasm The vacuole bound glycogen as well as the free cytoplasmic glycogen is digested by amylase in vitro It appears therefore that the lysosomes have accumulated glycogen and have been unable to subsequently utilize this glycogen It is proposed that this is due to the absence of an alpha glucosidase in these lysosomes which normally would have readily hydrolyzed the glycogen

Similar electron microscopic studies were carried out on the heart and skeletal muscle from the patient With certain reservations concerning fixation with formalin and possible postmortem changes a few reasonable comments can be made concerning these tissues In Fig 4 a representative section of heart is illustrated This is a longitudinal section and about the nucleus there are several vacuoles of granular material resembling glycogen as it would appear in more properly fixed specimens These masses of material are incompletely surrounded by a membrane Allowing for artifacts in preservation caused by formalin fixation one can assume that these masses may have been completely surrounded by a membrane similar to that shown for the liver Certainly it can be said that in the heart of this patient there was the accumulation of masses of cytoplasmic material presumably glycogen and that here too this material may have been within lysosomes

Aside from the pathologic changes described thus far the most striking changes at least histologically were seen in skeletal muscles (Fig 5) As is true in most cases of generalized glycogenosis the skeletal muscles of this child were grossly unremarkable However microscopically there was widespread vacuolar dilatation and degeneration of long segments of myofibers with clumps of basophilic material at the periphery of the fiber Frequently webs



Fig. 4. Electron micrograph of heart in generalized glycogenosis. There are several acinolar masses near the nucleus composed of finely granular material and partially surrounded by membrane. There is preservation of the normal myofibrillar pattern. Phosphotungstic acid. ×10,000

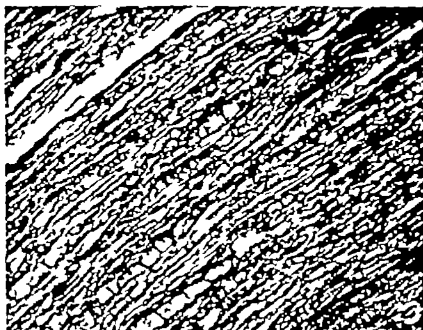


Fig 5 Skeletal muscle in generalized glycogenosis There is widespread vacuolar degeneration with accumulations of acid mucopolysaccharides in the myofibers Hematoxylin and eosin ×120

of this material extended across the damaged fibers and the nuclei in these areas appeared to be pyknotic Much glycogen could be demonstrated in these damaged cells by histochemical methods as well as in the adjacent more normal fibers Other staining techniques showed that these damaged fibers contained an acid mucopolysaccharide present in the basophilic material as seen with hematoxylin and eosin Fig 6 shows the electron microscopic features of skeletal muscle fibers in this patient In the upper right hand corner is a portion of an adjacent normal fiber which shows good preservation of the myofibrillar structure In the damaged fiber there are masses of granular material surrounded by fragments of a membrane as was demonstrated in the heart In addition there is a conglomeration of material composed of portions of granular material adjacent to the sarcolemmal membrane Occasionally this material extends in strands or masses across the fiber The location of this material coincides with the position of the acid mucopolysaccharides as seen by light microscopy These changes are not unlike that seen in early necrosis of muscle One thing is clear from these electron microscopic studies that is it appears that pathologically the skeletal muscle is more severely damaged than is the heart whereas clinically the cardiac changes are far more striking

In closing I would like to emphasize again that this disease is not merely glycogen storage disease of the heart but rather is a manifestation of widespread impairment in glycogen metabolism affecting many organs and tissues Whether widespread accumulation of glycogen in other organs leads to functional impairment is difficult to determine But it would seem to be more appropriate to refer to this disease as generalized glycogenosis rather than glycogen storage disease of the heart

DR SIDBURY The pertinent biochemical findings on the postmortem tissues (Table I) are the markedly elevated concentrations of glycogen in the tissues and the absence of acid (lysosomal) alpha glucosidase The glycogen is normal as characterized by beta amylase The phosphorylase values are lower than those values found in biopsied tissue as expected It is of interest that the kidney has the least glycogen of those organs which might be expected to



Fig. 4 Electron microscopy of skeletal muscle in generalized glycogenosis. There are several vacuoles containing finely granular material and partially surrounded by a membrane. There is also a conglomerate of granular material and mitochondria and absence of normal myofibrillar pattern. A portion of a more normal myofiber is in upper right hand corner. Phosphotungstic acid ×10,000

*Table I. Biochemical studies*

| | Normal | | Patient | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *Liver* | *Muscle* | *Liver* | *Muscle* | *Heart* | *Kidney* | *Spleen* | *Pancreas* |
| Glycogen content, per cent (wet weight) | < 6 | < 1.5 | 6.3 | 9.0 | 8.2 | 1.5 | 1.34 | 0.5 |
| Beta amylase degradation, per cent | 35-52 | 35-52 | 45 | 46.5 | | | | |
| Alpha-glucosidase (acid maltase) | + | + | 0 | 0 | 0 | 0 | | |
| Glucose-6-phosphatase | > 1.5 | | 3.77 | | | | | |
| Phosphorylase + AMP | | > 20 | 6.5 | 12.4 | 19.1 | | | |
| Phosphorylase − AMP | | > 5 | 4.7 | 10.9 | 3.6 | | | |
| P-Glucomutase + G-1, 6-P | 20 | 25 | 36.2 | 22.1 | 17.2 | | | |
| G-O Transaminase | > 20 | > 75 | 25.7 | 37 | 40.5 | | | |
| G-T Transaminase | > 3.0 | | 9.6 | | | | | |

[illegible]

*Table II. Family data in Type II glycogenosis*

| Series | Number of families | Number of children | Number affected | Per cent males | Consanguineous marriages | Per cent |
|---|---|---|---|---|---|---|
| Present study | 24 | 86 | 38 | 58 | 1 | 4.2 |
| Literature | 59 | 164 | 84 | 60 | 7 | 12.0 |
| Total | 83 | 250 | 122 | 59 | 8 | 9.8 |

have a marked accumulation. This is consistently true in these patients and we have no explanation for it.

The defect then has been defined in Type II glycogenosis as an absence of the lysosomal glucosidase. Recall now the constellation of symptoms and findings as exemplified by this case presentation. It is very difficult to reconcile the enzyme defect with the findings and early death. On electron microscopy the lysosomal membrane appears to have a very simple structure and one wonders whether the constituent enzymes might not be an integral part of the membrane. The implication would be that the absence of one of the constituent enzymes would then affect the lysosomal membrane structure and function. The malfunctioning lysosome could then be more readily visualized as resulting in the clinical dysfunction noted in the light of alteration of lysosomal enzymes found in the nutritional dystrophy of chickens.

We have assayed the acid alpha glucosidase activity in 6 siblings of patients with Type II glycogenosis and 4 who had normal activity in the cord and placenta are well today. This was the first infant whose cord showed an absence of the enzyme. Further experience is needed but it would appear that this will be a useful tool for early diagnosis. The value of this prognostic information can be appreciated fully only by the physician who has cared for affected siblings. The early diagnosis can spare the parents the anguish of reliving the course of the first affected infant for the months until the status of the subsequent infant is established.

Most of the diseases resulting from a detectable enzymatic defect in children have a genetic basis and generally the mode of transmission is recessive. Table II is a tabulation of the familial occurrence from our experience and that reported in the literature (stillborn infants excluded). Obviously, parents and grandparents could not be affected since the disease is lethal in the early years of life; hence only siblings would be at risk. It will be seen that the incidence in families with an affected child is approximately 50 per cent, which is twice the predicted 25 per cent of the Mendelian ratio for recessives. By the method of deletion of the proband, the expected 25 per cent expected in these families is very nearly achieved here. Noteworthy also is the distinctly increased incidence of consanguineous marriages in these families when compared with the general population, further supporting the postulation of a recessive condition.

An attempt has been made to estimate the gene frequency in North Carolina, which has a relatively stable population. Information was solicited in regard to such patients from pediatricians and pathologists throughout the State, and the records of the State Vital Statistics Division were canvassed. There were 1,560,679 live births between 1950 and 1963, and 4 patients with the disease were detected during this period. This would give a frequency of the disease of about 1 in 400,000 live births or 1 heterozygote in 300 persons.

Theoretically, the most hopeful approach to therapy would be the administration of an agent which would make the lysosomes leaky and either permit the glycogen to leak out or glycogenolytic enzymes to gain ingress. Such an agent might be administered from time to time. One of the less toxic detergents may qualify, but careful animal toxicity data would be needed before such an approach was attempted.

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# Fundamentals of clinical cardiology

## Enzymatic profile of myocardial infarct

*John G. Batsakis, M.D.**
*Russell O. Briere, M.D.***
*Ann Arbor, Mich.*

And thick and fast they came at last
And more and more and more

*Alice Through the Looking Glass*
*Lewis Carroll*

The causal relationship between the rise in activity of certain enzymes in the serum and the occurrence of damage to the myocardium has been established without question. Experiments and histochemical investigations have shown that infarcted heart muscle is rapidly depleted of various enzymes and that these enzymes appear in an active form in the blood that drains from the infarcted myocardium.

Rapid clinical utilization of these observations followed the report by LaDue and associates[1] in 1954 that serum glutamic oxalacetic transaminase (SGOT) is elevated after an acute myocardial infarct. As indicated in the preamble to this report, many other enzymes have been tested for their applicability in the confirmation of the diagnosis of myocardial infarct. The myocardium is a rich source of enzymes, and in addition to SGOT, elevations of the malate and lactate dehydrogenases, aldolase, phosphoglucose isomerase, and creatine phosphokinase are usually present after infarction of cardiac muscle.

To the present time, however, only five enzymatic assays have withstood critical clinical and laboratory investigation. These are the measurement of (1) serum glutamic oxalacetic transaminase (SGOT), (2) serum lactic dehydrogenase (SLD), (3) isoenzymes of serum lactic dehydrogenase, (4) serum α-hydroxybutyric dehydrogenase (SHBD), and (5) serum creatine phosphokinase (SCPK).

*Transaminases.* Human tissues and serum contain two transaminases of clinical importance, SGOT and glutamate pyruvate transaminase (GPT). They catalyze the reversible transfer of an amino ($NH_2$) group from an amino acid to a receptor keto acid, yielding a new amino acid and a new keto acid.

$$\text{Aspartate} + \text{ketoglutarate} \xrightleftharpoons{\text{GOT}} \text{Glutamate} + \text{oxalacetate}$$

$$\text{Alanine} + \text{ketoglutarate} \xrightleftharpoons{\text{GPT}} \text{Glutarate} + \text{pyruvate}$$

The heart and liver are especially plentiful in GOT, but the liver contains much more GPT than does the heart. Thus the SGOT may be expected to be increased when either of these organs is damaged, but an elevation of SGPT is typical of hepatocellular damage only.

*Lactic dehydrogenase.* This enzyme is widely distributed throughout most body tissues and catalyzes the reaction

$$\text{Lactate} + \text{nicotinamide-adenine dinucleotide (NAD)} \xrightleftharpoons{\text{LDH}} \text{pyruvate} + \text{reduced nicotinamide-adenine dinucleotide } (NADH_2)$$

From the [illegible] University of Michigan, Ann Arbor, Mich.
Received for publication Dec. 13, [illegible]
*Associate Professor of Pathology
**Assistant Professor of Pathology

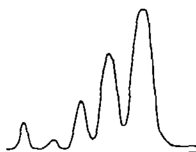


Fig 1 Densitometric tracing of a lactic dehydrogenase electropherogram obtained from a patient manifesting an acute myocardial infarct Note (1) the elevated fast (anodic) isoenzymes and (2) the clear discrimination between these myocardial fractions and the cathodic hepatic isoenzymes

*Lactic dehydrogenase isoenzymes* Lactic dehydrogenase in consort with other enzymes is not a uniform enzyme but rather occurs in a number of molecular species These differ in their primary structure i e amino acid sequence yet possess the same action and substrate specificity (L lactate) The enzymatically active fractions (isoenzymes or isozymes) can be separated by a variety of means Under the conditions of electrophoresis (starch gel agar gel or cellulose acetate) normal human serum is separable into five distinct isoenzymes [3] Tissues with a high aerobic metabolism such as cardiac muscle have a high content of fast migrating (anodic) isoenzymes Conversely slow migrating (cathodic) fractions predominate in the liver [3] The heart and liver fractions occupy extreme poles of the isogram and may be readily distinguished (Fig 1)

The five isoenzymes are produced by a random tetrameric association of two different polypeptide subunits which are considered to be under separate genetic control [4] The first and fifth are homogeneous tetramers whereas the three intermediate bands are heterogeneous or hybrid forms This suggests that in fact only two principal or parent forms of LDH exist All possible combinations of these two monomers are produced (Table 1)

The clinical laboratory and diagnostic importance of this molecular heterogeneity lies in the fact that a differential evaluation of an elevated total SLD may be possible

*Table I Tetramic molecular association of the two principal polypeptide subunits of lactic dehydrogenase*

Monomers

A B

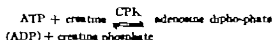
Tetramers

| | | | | |
|---|---|---|---|---|
| AA<br>AA | AB<br>AA | AB<br>AB | BB<br>AB | BB<br>BB |
| LDH | $LDH_2$ | LDH | LDH | $LDH_5$ |

when there is concomitant injury to several tissues

*Alpha hydroxybutyric dehydrogenase* (*HBD*) It has been shown that lactic dehydrogenase does not possess an absolute specificity for its usual substrate but can also convert the oxo group of ketobutyric acid in the alpha position to the hydroxy group [5] The fast migrating SLD isoenzymes exhibit much greater ability than do the slow fractions to reduce $\alpha$ ketobutyrate relative to their activities with pyruvate as substrate In deference to the reaction with $\alpha$ ketobutyrate the catalyst has been designated $\alpha$ hydroxybutyric dehydrogenase (HBD) [6] At present it is not known what kind of enzyme one is measuring when the assay for SHBD activity is performed but the measurement has been equated with a chemical differentiation of the fast migrating SLD isoenzymes [6]

*Creatine phosphokinase* (CPK) CPK catalyzes the reversible transfer of a high energy phosphate group from adenosine triphosphate (ATP) to creatine



ATP + creatine $\xrightarrow{CPK}$ adenosine diphosphate (ADP) + creatine phosphate

The enzyme is found principally in skeletal and heart muscle and also in lesser amounts in brain tissue Kidney liver lung pancreas and the erythrocytes have virtually undetectable amounts of CPK activity [7] The distribution in human tissue has led to the consideration of serum CPK activity as the most specific and sensitive serum enzyme test currently available for the confirmation of disease or injury to

skeletal muscle and myocardium.[7] In diseases of skeletal muscle with particular reference to the dystrophies, the estimation of CPK is the measurement of choice and studies in patients with muscular disorders underscore the value of estimation of CPK in the differential diagnosis between progressive muscular dystrophy and atrophies of neurogenic origin.[8]

## Clinical application

Any evaluation of the clinical applicability of an enzyme assay must perforce be a consideration in three fundamental and interrelated areas of consideration: (1) ease of assimilation into the diagnostic laboratory, (2) specificity and sensitivity of the enzyme being measured, and (3) duration of the enzyme's activity in serum after tissue injury.

*Laboratory performance.* The estimation of the activity of SGOT, SLD, and SHBD may be determined satisfactorily by either spectrophotometric or colorimetric assays. The former has inherent chemistry advantages but equal *clinical* information is derived from both types of assay. As of the present, colorimetric assays of CPK cannot be recommended and are distinctly inferior to ultraviolet spectrophotometric methods.[9]

The electrophoretic separation of SLD isoenzymes is diagnostically superior to techniques relying on heat stability of the fractions. Cellulose acetate fractionation is within the technical ability of any routine laboratory and is readily suited for either a quantitative or qualitative evaluation after separation of the isoenzymes.[8]

*Enzyme specificity.* There is no enzyme activity measurable in serum which is specific for heart muscle alone. Specificity then becomes a subject of relative evaluation. In decreasing order of relative specificity, the enzymes may be listed as follows: CPK, isoenzyme of LDH, SHBD, SGOT, and SLD.

The nonspecificity of SLD is well known. Table II, listing the tissue activity levels of CPK and GOT, may be considered to represent the two extremes of the relative specificity scale. Table III emphasizes the absence of CPK activity within the erythrocyte, a very important feature when one is considering the effect of hemolysis on serum activity levels.

Early reports attested to a high degree of specificity for heart muscle manifested by α-hydroxybutyric dehydrogenase.[10,11] As clinical and diagnostic experience with the assay was gained, this enhanced specificity was found to be only relative, albeit superior to the measurements of SGOT and SLD.[8] Fig. 2 indicates that elevations above normal may occur in a variety of disorders other than myocardial infarct. Elliott and Wilkinson[8] have resorted to the use of an SHBD/SLD ratio in the differentiation of myocardial disease from other disorders in which the SHBD is elevated. Investigation in our laboratories[8] and that of Rosalki[13] have not substantiated this discriminatory capacity of the ratio.

Fractionation of the isoenzymes of lactic dehydrogenase has markedly increased the sensitivity and specificity of that enzyme in clinical diagnosis. The various fractions have been designated numerically according to their primary sources as follows:[13]

*Table* II

| *GOT activities of human tissues** | | *CPK activities of human tissues†* | |
|---|---|---|---|
| Heart | 7 800 | Skeletal muscle | 18 400 |
| Liver | 7 100 | Heart | 5 550 |
| Skeletal muscle | 5 000 | Brain | 3 400 |
| Kidneys | 4 500 | Adrenal gland | 136 |
| Pancreas | 1 400 | Lung | 0 5 |
| Spleen | 00 | Liver | 0 |
| Lung | 500 | Prostate | 0 |
| Red blood cell | 15 | Red blood cell | 0 |
| Serum | 1 | Serum | 0 |

*Rel[illegible]

†Expr[illegible] (x 10)/mg)

*Table* III *Normal erythrocyte and serum content of enzyme activity*

| | *GOT* | *LDH* | *HBD* | *CPK* |
|---|---|---|---|---|
| RBC/serum content | 8/1 | 1 000/1 | 1 000/1 | 0 |

S H B D ACTIVITY LEVELS IN CLINICAL DISORDERS

Fig. 2. Although SHBD activity may be considered to be more specific for myocardial lesions than the SGOT or SLD, false positive levels are seen in hepatobiliary disorders, congestive heart failure, and hematopoietic disorders, especially hemolyses. Note, however, the absence of false negatives in the 66 cases of documented myocardial infarct. In the University of Michigan series all infarcts have produced activity levels above 120 milliunits.

1 from skeletal muscle and liver, 2 and 3 from lungs, 3 and 5 from the pancreas, 3 and 4 from the lungs, 3, 4, and 5 from the kidney, 4 and 5 from cardiac muscle.

In actual laboratory and clinical practice similar and often identical patterns for myocardial infarct are seen in patients manifesting infarcts of the kidney, patients with pernicious anemia or lymphomas with hemolytic anemia, and patients suffering from progressive muscular dystrophy.[4] To emphasize the effect of hemolysis, a common practice is to use hemolyzed serum as a positive control for electrophoretic separations.

*Enzyme sensitivity.* Under the proper conditions of appropriate selection of test and due consideration of the duration of activity in sera, all five procedures will yield positive results. False negatives are rare and may be attributed to laboratory error in most instances.[14] SLD isoenzyme fractionation appears to have a superior sensitivity. The appearance of a positive increase in the first fractions may antedate both electrocardiographic changes and a rise in the total enzyme activity in the serum. Ten from our series of over 2,000 isograms have manifested this phenomenon, and the experience of Freeman and Opher[13] corroborates these observations.

Reliance on the estimation of the total activity in sera alone may be misleading in the discrimination between superimposed congestive heart failure and a second infarct or extension of the primary myocardial infarct. In these instances isoenzyme fractionation and/or estimation of CPK offer considerable assistance, in the former by the emergence of a hepatic band in the isogram and in the latter by an additional peaking after normalization has occurred. The absence of CPK in the liver makes a secondary rise in activity almost pathognomonic of a superimposed or extended myocardial infarct.

*Enzyme release and duration of activity.* After an initial elevation following myocardial infarction, enzyme activity in serum declines rather rapidly and

*Table IV. Reaction time or release activity span in serum after uncomplicated myocardial infarction*

| Enzyme activity in serum | SGOT | SLD | SHBD | SCPK |
|---|---|---|---|---|
| Onset of rise | 12 hr | 12 24 hr | 12 24 hr | 3-4 hr |
| Return to normal | 4 days | 7 days | 10 days | 3 days |
| Peak X normal | 4 2 | 3 6 | 4 8 | 11 |
| Time of peak | 24 hr | 72 hr | 72 hr | 33 hr |

lives of the enzymes important in the diagnosis of myocardial infarct are short i e the enzymes are rapidly eliminated or inactivated It may be seen then that although a normal serum activity level in the course of serial determinations excludes the presence of a fresh or superimposed infarct it does not depending upon the time of collection exclude the diagnosis of an initial myocardial infarct

Table IV summarizes the average time reaction span and peaks of the serum activity of four of the five enzyme assays under consideration After a myocardial infarction activity increases in the serum in the following order (1) CPK (2) GOT (3) LD and (4) HBD The return to normal levels also follows this sequence Serum CPK begins to rise before any of the others often as early as 3 to 4 hours after the infarction Peak activity is usually reached at 36 hours followed by a rather precipitous drop to normal levels by the second to the fourth day The length of time during which SGOT is elevated after the infarction is relatively short—average of 4 to 5 days—and although SLD is elevated for a longer time SHBD remains at abnormal levels the longest—10 to 15 days Large myocardial infarcts may cause persistence of abnormal levels of SHBD for as long as 5 to 10 days after the total enzyme activity of SLD has normalized[13,14] (Fig 3) If restricted to the choice of one specimen it would appear to be wisest to delay sampling until the period 24 to 36 hours after infarction It is this time period which will give the greatest likelihood of obtaining abnormal values for all enzyme activity

## Conclusions

There is no enzyme activity measurable in serum which is specific for myocardial

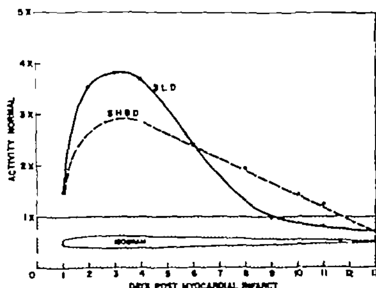



Fig 3 Graphic depiction of serial isoenzymes and SLD and SHBD activities in the serum from a patient manifesting an uncomplicated myocardial infarct Note the persistence of elevated levels of SHBD and positive isogram after the normalization of SLD

infarction Of the five most applicable enzymatic procedures (SGOT SLD, SLD isoenzymes SHBD and CPK) for the confirmation of the diagnosis of myocardial infarct the estimations of CPK and the fractionation of SLD isoenzymes enjoy the greatest degrees of specificity and sensitivity

Specificity and sensitivity notwithstanding the *single* most important variable in the diagnostic application of the tests is the time of collection of the sample in relation to the clinical history False negatives are the rare exception if the appropriate test is used in the light of activity spans in serum

Estimations of CPK are most useful in the acute clinical situations since a rise in its activity may precede that of the other enzymes by 8 hours All measurements will be positive within 24 to 36 hours after the onset of the infarction The major significance of estimations of SHBD resides in the fact that its activity persists after other activity levels have returned to normal

Isoenzyme fractionation and serial estimations of CPK because of their enhanced discriminatory ability are superior to all other enzyme tests for purposes of differential diagnosis and prognostic follow up evaluation

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# Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Alan F. Lyon

## Antianginal drugs
## Part VII. Miscellaneous drugs

*Solomon Fisch, M.D.**
*Bronx, N. Y.*

The number of drugs that have been proposed for the treatment of angina in addition to those already discussed in this series is myriad. Some of them have fallen into disrepute. Others defy rational explanation for their presumed antianginal efficacy.

*1. The non-nitrate long-acting vasodilators.* These include dipyridamole (Persantin) (see American Heart Journal 65:423-424, March 1963), prenylamine (Segontin), and a benzofurane derivative (Amplivix). Only dipyridamole is available in this country. The other two are still experimental in this country but are available for clinical use in Europe. They all share the property of producing coronary vasodilation in experimental animals when given parenterally. Most of the studies which report favorable results with these agents have been uncontrolled. In controlled experimental work, it has been found that when given orally they are devoid of antianginal efficacy when compared with placebo. Accordingly, none of these agents can be recommended for use in angina pectoris.

*2. Psychotropic agents.* Besides the barbiturates like phenobarbital or Butisol, other agents such as chlordiazepoxide (Librium) and meprobamate (Equanil or Miltown) have been advocated for use in angina pectoris. It has not been proved that patients with angina pectoris suffer from more anxiety than a comparable population which does not have angina pectoris. It has been conjectured, however, that when anxiety is present there may be an adverse effect not only on angina pectoris but on arteriosclerotic heart disease in general. This has not been proved. No controlled data are available to indicate that these agents have any specific effect on angina pectoris.

*3. Digitalis and diuretics.* It has often been observed clinically that when congestive heart failure supervenes, angina pectoris decreases. Sir James Mackenzie was the first to call this to the attention of the medical profession many years ago. The usual explanation given is that heart failure imposes a restriction on the activity of the patient, which in turn decreases the frequency of episodes of angina. These observations are difficult to reconcile with those of other clinical studies in which digitalis has been noted to be effective in the treatment of nocturnal angina. In these cases it seems to be reasonable to assume that digitalis works by decreasing congestive heart failure. Catheterization studies have demonstrated that the pulmonary artery wedge pressure rises during some attacks of angina, that is, heart failure appears with angina. In general, however, it is thought that digitalis does

Received for publication April 29, 1966.
*Director, Cardiac Therapy Research Unit, Bronx Veterans Administration Hospital, 130 West Kingsbridge Road, Bronx, N. Y. 10468.

not have a significant antianginal effect in the usual patient. The use of digitalis as antianginal therapy awaits final assessment by carefully controlled double blind studies.

There are some studies which indicate that diuretics like meralluride (Mercuhydrin) or chlorothiazide (Diuril) relieve angina pectoris. It is difficult, however, to compare a placebo with a potent diuretic without the introduction of bias. Further work is needed with these drugs.

*4 Miscellaneous agents.* Alcohol (first advocated by Heberden), quinidine, anticoagulants, griseofulvin (Fulvicin and Grisactin) and antithyroid agents such as imidazole (Tapazole) or propylthiouracil are some among many of a heterogeneous group of drugs reportedly useful in angina pectoris therapy. That so many agents with such diverse pharmacologic properties have been reported to be of benefit in angina pectoris reinforces the conclusion that placebo reaction in angina pectoris is a formidable and real problem that makes assay of efficacy most difficult. There are no significant, well controlled studies that attest to the efficacy of any of the above-mentioned therapies.

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# Annotations

## Shock after acute myocardial infarction

It has long been recognized that a number of patients hospitalized for treatment of acute myocardial infarction develop the clinical syndrome of shock. The proportion of patients in whom this complication arises has varied widely in different reported series, largely because of varying criteria for the definition of shock. In general, when the criteria for selection are stringent, the incidence of shock is lower and the fatality higher than when less stringent criteria are used; thus the proportion of patients dying from this complication is in relative agreement and constitutes between 11 and 19 per cent of admissions.

Lack of uniformity in the adoption of criteria for the diagnosis of cardiogenic shock has likewise led to conflicting reports on the beneficial effects of various therapeutic procedures, notably the infusion of pressor amine substances. It is clear that the level of the arterial blood pressure alone does not always offer a reliable guide to the adequacy of tissue perfusion and hence oxygenation, which is the sine qua non of the shocked state. This is further complicated by the earlier and freer use of pressor amines, often given prior to admission of the patient to hospital, which may prevent the blood pressure from falling to shock levels despite gross depression of the cardiac output and obvious clinical signs of inadequate peripheral blood flow.

Despite numerous clinical and pathologic investigations, it is still not clear why certain patients are prone to develop the syndrome of shock after acute myocardial infarction whereas others develop acute left ventricular failure. Neither age, sex, location, nor extent of the infarction appears to correlate well with the development of shock, although it has recently been suggested that death from this complication is less likely to occur in patients with pathologic evidence of remote infarction at autopsy. Still less is known concerning the fundamental pathophysiologic disturbances which lead to the hemodynamic characteristics of shock in man, namely, hypotension associated with severe depression of the cardiac output. In the past this has led to a polemic in the medical literature on the relative importance of abnormalities of myocardial function (central shock) and of alterations in the control of the peripheral circulation (peripheral circulatory failure). Much of this discussion stemmed from a paucity of data in patients, since their precarious condition usually precluded thorough hemodynamic assessment, and also from difficulty in obtaining a suitable experimental model for study of the condition in animals. The former difficulty has been overcome by the development of more subtle techniques for the study of the circulation, and the latter by the introduction by Agress of a method of reproducing cardiogenic shock in dogs by means of diffuse coronary embolization.

As is so often the case, it now seems to be clear that the proponents of both theories concerning the mechanism of cardiogenic shock were in part correct. Although it is true that pressures within the lesser circulation are rarely elevated to levels commonly associated with left ventricular failure, a study of ventricular function in experimental cardiogenic shock in dogs reveals a grossly abnormal relationship between ventricular work and filling pressure; the ventricular function curve in these animals is flattened, so that only minor increases in stroke work are obtained by relatively large increases in filling pressure. Teleologically, it would appear to be desirable that the organism maintain a relatively low left ventricular end-diastolic pressure rather than risk the development of pulmonary edema in order to gain a small increase in ventricular work. The mechanism whereby venous return is adjusted to prevent further increase in pressures within the lesser circulation is unknown, but the demonstration by Salisbury that sudden distention of the left ventricle causes reflex pooling of blood in the capacitance vessels suggests a possible mechanism in man. The apparent paradox in the hemodynamic disturbance in these patients might best be described as masked left ventricular failure.

Bearing in mind these pathophysiologic changes, we can define the objectives to be sought in treating this condition. These are, first, to restore and maintain an adequate arterial pressure, and second, to effect an optimum improvement in ventricular function. The first of these objectives is generally regarded as taking precedence in the belief that maintenance of an adequate perfusion pressure to the brain, kidneys, and the heart itself is of prime importance. For this reason, intravenous norepinephrine, a drug with strong vasoconstrictor properties, has been most frequently employed in treating this condition in recent years. Although many investigators have reported a reduction in mortality in patients treated with this agent, others have noted no significant difference between treated and untreated groups. When cardiac output has been determined in severely shocked patients, it has almost always been reduced out of proportion to the reduction in mean arterial pressure; the calculated total peripheral resistance has been high. Restoration of this situation toward normal must therefore presuppose a fall in total peripheral resistance, and the rationale for employment of a drug with strong vasoconstrictive properties has been questioned. It would appear to be logical to place priority on

effecting an optimum increase in myocardial con tractility while ensuring an adequate venous return so that arterial blood pres ure may be raised by means of increasing cardiac output This reasoning has led some investigators to suggest that inotropic agents such as the digitalis glycosides which are largely devoid of peripheral vasoconstrictor effect should first be employed In experimental cardiogenic shock rapid digitalization has proved to be superior to the infusion of norepinephrine in terms of raising the cardiac output without further increasing the left ventricular end-diastolic pressure The hazard of digitalis excess mu t be carefully considered but the frequency of digitalis induced arrhythmias after acute myocardial infarction appears to be no greater than in other cardiac emergencies requiring its use.

It would seem to be dangerous to attempt to generalize in recommending any specific therapy in the treatment of cardiogenic shock Id ally these patients hould be cared for in a special treatment area with appropriate facilities for measuring all a pect of circulatory function The placement of catheters in the superior vena cava and radial artery permit the monitoring of central enous and arterial blood pressures as well as the rapid estimation of cardiac output by the ind cator-dilution method In thi w y the hemodynamic effect of ny pecific therapeutic measure can be rapidly assessed It hould be emphasized that general measures in the deeply shocked patient are equally as important as the choice of a specific therapeutic agent Electrolyte disturbances acidosis and arterial unsaturation should be quickly recognized and corrected Electrocardiographic monitoring with appropriate control of cardiac arrhythmias should they develop is essential to the total management of these critically ill patients No doubt when more data appear from intensive care areas such as the one described a clearer understanding will emerge of the therapeutic rationale in thi serious complication of acute myocardial infarction which now claims such an alarming mortality

*R F P Cronin M D F R C P (C)*
*Assistant Prof of Medicine and Physiology*
*McGill University*
*Montreal Que Canada*

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# Transvenous pacing of the phrenic nerves

In September 1964 this group observed that the right phren nerve could be stimulated from the superior vena ca In a patient undergoing transvenous right ventricular pacing with an external pulse generator card ac re ponse cea ed and rhythm contractions of the upper abdominal muscles dev loped simultaneou ly Physical examination revealed a rate of 42 and a pacemaker rate coincident with the abdominal contractions of 72 The ECG demonstrated 2 1 heart block w th no response to the regularly reco de l pacemaker impulses The subcutaneous catheter retent on sut es had been extruded nd the t p of the catheter had been d pl ced proximall to the mid superior vena ca a Fluoroscop cally the right d phragmat c leaf showed rhythmic co tract ns co nc dent with the pacemaker impulse which ceased when the pacemaker was turned off nd d d not resume when cardiac pacing was re t tarted f om the right ventricle

S nce thi time the right diaphragm of 10 dogs and 10 patients hav been paced acut experiments by 2 msec card ac pacemaker impulses ap pl ed to the mid uperior ena ca Regular pa mod c contractions were secured at rates ranging from 45 to 70 per minute and currents ranging from 3 to 12 m lliamperes w th immediate return to normal e p ration when pacing was discont nued Card ac action was not disturbed by these activit es

Exploration of a transvenous approach to the left phrenic nerve is now under way One pat ent has responded to cardiac st mulatory impulses administered to the left phrenic nerv through the main pulmonary artery Several others however

Work supported by U ited States Publ Heal h Serv ce Gra t No. HE-08666-04

*Table II. Over-all comparison: Q, R, and S versus 10, 40, 60 msec. vectors*

| Vectors | Angles | | | Voltages | | |
|---|---|---|---|---|---|---|
| | *Normal FD curves* | *Smaller range* | *Less variance* | *Normal FD curves* | *Smaller range* | *Smaller coefficient of variation* |
| Q, R, and S | 9 | 7 | 8 | 7 | 5 | 6 |
| 10, 40, 60 msec. | 4 | 2 | 1 | 8 | 7 | 5 |

*Three significant at $p < .05$ or greater.

Table I compares mean (M), standard deviation (SD), range (R), and coefficient of variation (CV) or variance ratio (F) for paired sets of data. Range is the crudest of the tests since it does not reflect the frequency of observations at each value. It has been calculated for 96 per cent of observations by eliminating the single highest and lowest measurements. This should approximate M ± 2SD if distribution is normal. Its unit is in degrees (angles) or millivolts (voltage) and represents the difference between the highest and lowest of 48 observations. F (larger SD²/smaller SD²), a two-tailed test of variance, is appropriate to compare the distribution of angular measurements since only the scatter about the mean is of interest and the values for M and SD are unrelated. F is not suitable, however, for the voltage comparisons since values for M and SD are related (larger M tend to have larger SD). CV is used because it takes this into account. Normality of frequency distribution (skewness and kurtosis) was tested at the 0.5 level of significance by Snedecor's method. Most of the calculations were performed by computer programs on the IBM 1620 unit.

Table II indicates over-all comparison of the two methods with data for M vector excluded. The number of angular measurements which generated normal frequency distribution curves, smaller ranges, and less variance distinctly favors the morphologically identified vectors. Comparison of Q and R angles with those of 10 and 40 msec. vectors consistently favors the former although only one of six F values reaches a level of significance. The S vector angle was also more stable than the 60 msec. vector in all except the frontal plane where both showed a very wide scatter. The values for the M vector angle scatter more widely than those of either the R or 40 msec. vectors. Differences in the voltage measurements, however, are not impressive. Those for the Q-10 msec. vector pair are very similar but CV are slightly smaller for the timed vector in all four. CVs for the R and S voltage, however, are smaller than those of their counterpart in six of the seven instances in which they differed.

In conclusion, it appears that morphologically defined vectors Q, R, and S can be identified with acceptable consistency in normal loops and when compared to consecutive timed vectors at 10, 40, and 60 msec., satisfactory ranges of angles and voltages are evident. Their angular positions were somewhat more stable than those of the timed vectors, whereas scatter of values for voltage was approximately similar. The position of the M (maximum) vector in each plane was less predictable than that of either of the other two mid-loop vectors (R and 40 msec.), but its voltage range was equally as acceptable.

*J. Calhoun Witham, M.D.*
*Division of Cardiology*
*Medical College of Georgia*
*Augusta, Ga. 30902*

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# Practical remarks on the McFee and Parungao VCG lead system

There is no intention here of debating at length the superiority of the different systems of lead proposed for vectorcardiography. However one must stress the fact that an increasing number of investigators give preference to so-called orthogonalized systems of lead based on the lead field concept and using multiple electrodes to neutralize proximity effects. Among such systems the ones of Schmitt[1] of Frank and of McFee and Parungao[2] are well known. They are in fairly good agreement with regard to the wave forms of the VCG tracings that they provide. We now have 3 years of personal experience with the McFee system. In a series of 15 cases both normal and abnormal comparisons between the Frank and the McFee methods gave us results that were sufficiently equal so that we could adopt without mental reservation either the one or the other provided that the electrodes are placed precisely. However we adopted the McFee system and this for additional reasons which are mentioned below.

One remark in McFee's original paper with regard to comparison between Frank and their own procedure convinced us of the greater reliability of the latter method for routine clinical use. It deals with the variations in the location of the electrodes and their consequences on the reproducibility of the tracings in each system. Inaccuracy or error in the location of anterior or lateral thoracic electrodes proved to be less disadvantageous when the McFee rather than the Frank system is used. This tendency to more distortion with a similar amount of original error in electrode placement seemed to us to be of decisive importance in clinical application. The existence of less error with the McFee system for the same degree of precision in the application of the electrodes to the skin probably is due to the fact that the frontal tripolar electrodes of the McFee system and the left lateral bipolar electrodes as well cover a relatively larger vertical field distance along the roughly cylindrical surface of the thorax. Thus a longitudinal displacement has fewer consequences when the McFee electrodes are used than when all electrodes as in Frank's system correspond to one single level. We have also tested in another way the limits of reliability of the McFee triple frontal electrodes with 3 units 20 mm in diameter located at the 3 corners of an equilateral triangle having a radius of 60 mm. By comparing two horizontal vectorcardiograms obtained according to McFee, one normally executed with the base of the triangle parallel to the transverse axis of the trunk and one after rotation of the triangle by 60 degrees, we found striking similarity and sometimes almost an equality of both figures in most of the experiments. 15 such experiments have been performed. The entirely different positioning of the 3 chest electrodes after a rotation of 60 degrees demonstrates the validity of the lead field concept in this particular case and represents a simple solution to the problem of using semidirect chest lead points to obtain an average lead largely suppressing proximity effects. We often took advantage of this winning trick on the occasion of VCG demonstrations to visitors and it never failed to persuade them of the astonishing validity of the principle.

McFee and Parungao, when presenting their new system of lead in this JOURNAL 4 years ago, emphasized its suitability for routine clinical application. They said that Frank's or Schmitt's systems, in spite of their sound theoretical bases, do not strike the optimum balance between accuracy and simplicity. They presented their new system of lead as an improvement in this balance. Our present opinion in the matter would be in agreement with theirs with one reservation: that is, not to use 9 separate suction electrodes as against Frank's 7 but instead to substitute for them plates of grouped electrodes according to the description which follows. For various and quite intelligible reasons 9 suction electrodes are very difficult to handle because of the need for their precise location on the chest according to an equilateral triangle of accurate dimension and their precise linear lateral location as well; this process implies the use of a special template which is unsuitable for a rapid application. This difficulty is doubtless the reason that this attractive system of VCG lead, so thoroughly tested by its authors, has not yet received the wide attention that it deserves according to our own experience.

By making a few practical changes we have greatly improved the routine application of the McFee system. These changes consist first in the maintenance in solid dependency of the three frontal unit electrodes 104 mm apart (= 60 mm radius) on a circular Plexiglas plate 15 cm in diameter and secondly application of the same system to the two lateral electrodes units 110 mm apart on a distinct Plexiglas plate. The latter is 14 cm long and narrow with a flat triangular shape (top triangle dimension 5 cm) to allow the addition of a third foot at mid-distance of the electrodes and within 2 cm parallax of their line of junction. This third foot is a 20-mm long Plexiglas cylinder the role of which is to maintain the whole surface of the plate parallel to the skin (see Fig. 1).

After careful determination and marking of the center points of the mounting position, both electrode assemblies, tripolar and bipolar, are easily fixed at the right place by the pressure of a rubber belt around the thorax. Pasting the metal electrodes with an adequate electrode jelly is then performed by forcing a finger tip smeared with paste below each unit. It is perhaps necessary to mention that previously the skin should be energetically rubbed with an alcoholized pad at all levels of application of electrodes. The same process is used for all four

Letter often expressed as M Fee ly



Fig. 1

other metal plate electrodes 6 by 5 cm placed on the right axilla back, left neck, and left thigh according to the McFee description

Each electrode assembly has a central terminal incorporated into the Plexiglas plate so that only one connection to the amplifiers for each is necessary. The resistances for these two small central terminals are respectively 100 000 and 66 000 ohms as suggested by the authors of the system. This grouping of 3 and 2 units of electrodes effectively reduces to 6 the total number of electrodes in the system. The regularity of the frontal triangle and its correct spacing as well as for the bipolar plate electrode are guaranteed in all cases. The quality of skin resistance and contact are brought to their best very simply. The pressure of the belt plays its part in assuring correct placement and contact. At the same time it helps to hold firmly the two other contacts on the right axilla and on the back. The lateral neck electrode is best affixed by the pressing action of a small sandbag 20 cm long and 6 cm in diameter.

Some details related to this grouping of electrodes deserve description. The first is concerned with the possibility of individually leveling each of the small silver unitary electrodes from their mounting points on the circular and on the recto-triangular Plexiglas plates. The object is to place them parallel to the surface of the skin the inclination of which varies at each level and with each patient. For that purpose each little circular unit electrode is fitted with a central stud 6 mm long and 5 mm in diameter. This stud is forced into a cylindrical tube of flexible plastic material 16 mm long which itself is gently plugged into a second stud fixed in the Plexiglas table. The ability to bend the mounted electrode with the finger permits all kinds of orientation of its flat surface with angles up to a maximum of 25 degrees. This procedure is easily executed once the tripolar and bipolar Plexiglas plates are inserted under the belt. In practice it is a self leveling manipulation that adjusts itself as the plate is applied to each electrode.

The second detail is concerned with the possibility of various spacings of the poles of the triple or double electrodes for a more proportionate adaptation to the body size in younger individuals. For that purpose both of our Plexiglas plates are equipped with a second set of studs having a closer spacing of 45 mm radius for the tripolar and 40 mm for the bipolar. The electrodes and their corresponding plastic tubes are pulled out from the outside studs and plugged into the inside ones. For small infants or babies we have a second and third set of tripolar and bipolar electrode assemblies with radii of 40 and 30 mm respectively.

This system of grouped electrodes has shown itself to be beneficial in every respect, use and results. I thus consider that the McFee and Parungao VCG method may compete successfully with all other sophisticated systems of clinical vectorcardiography now available. It has become a 6 electrode VCG corrected system among the least time consuming for application and most reliable according to the lead field concept.

Thus we hope to have given still more validity to the words of the authors when they state that the object of their system is to maximize accuracy and minimize complexity. By a most agreeable coincidence our modified version of the McFee system has been examined by Dr. McFee himself who happened to visit me at the time of preparation of this annotation. He states that he highly favors our method and intends to adopt it for use in his own laboratory.

*Pierre W. Duchosal, M.D.*
*Professor of Medicine*
*With technical assistance of*
*Raymond Pasche*
*Geneva University*
*Geneva, Switzerland*

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Address: 24 Boulevard des Philosophes, Geneva, Switzerland.

# Book reviews

THE FOETUS AND THE NEWBORN. RECENT RESEARCH. British Medical Bulletin Vol 22 No 1 January 1966 Edited by K. W. Cross and G. S. Dawes London 1966 Medical Department British Council 10? pages Price $5

The *British Medical Bulletin* continues to publish excellent issues. This one is no exception. The authors are expert in their fields and most of them are actively engaged in research in the problems that they summarize. Among the subjects presented are morphometry of human placenta, maintenance of isolated fetus, fetal growth retardation, immunity in fetus and newborn, biochemical aspects of newborn liver, resuscitation of the newborn infant and brown adipose tissue as well as other equally important and interesting subjects. This issue is highly recommended. It is authoritative, concise and well written.

HERZAUSKULTATION. By Rudolf Zuckermann ed 2 Leipzig 1965 Georg Thieme 535 pages 141 illustrations

The second enlarged edition of Zuckermann's book has appeared two years after the first edition which is evidence of its favorable acceptance. The volume is comprehensive and up to date. After discussion of the technique of auscultation of the relationship of normal heart sound to other events in the cardiac cycle and of their mechanism and normal standards (pp 1 74) murmurs are described with a discussion of their underlying mechanism and their changes with various diagnostic procedures (exercise, Valsalva and Muller maneuvers, vagal stimulation, liver and thorax compression and drug ). A table summarizes the effect of phenylephrine, norepinephrine and amyl nitrite on left and right cardiac murmurs in the diagnostic differentiation of various types of valvular heart disease (p 103). A short chapter (pp 104 112) is devoted to heart sounds in infants, children and adolescents. The major part of the book (pp 113-3 5) is a detailed discussion of heart sounds and murmurs in 124 (?) various pathologic conditions with emphasis on differential diagnosis.

Although Heart Auscultation is the title of the book, vascular sounds recorded from the neck, head, thorax, abdomen, extremities and eyes are also included (pp 2 6-7? ). The text suffers from a certain lack of uniformity and systematic organization in the actual printing.

The text is illustrated by numerous diagrams which are excellent for teaching purposes; actual phonocardiograms are shown in the last part (pp 331-443). Perhaps by an oversight these phonocardiographic illustrations are not numbered and there are no references in the legends to the text or vice versa. The bibliography (pp 43 516) is most complete and valuable, assembled by subject and alphabetically.

To the knowledge of this reviewer there is no English text which covers the field in the way this monograph does. It is of value to the medical student and resident as a text and to the cardiologist as a reference.

ELECTROCARDIOGRAPHY IN INFANTS AND CHILDREN. Edited by Donald E. Cassels M D and Robert F Ziegler M D New York 1966 Grune & Stratton Inc 366 pages Price $16 75

This book represents a summary of a symposium sponsored by the American College of Chest Physicians. The participants reviewed some of the important problems in clinical electrocardiography and vectorcardiography. Among the subjects presented in these proceedings are lead systems, relationship of the standard electrocardiogram to the vectorcardiogram, intracardiac electrocardiography, the normal electrocardiogram of infants and children and the electrocardiogram of arrhythmias, disease states such as left ventricular hypertrophy, a few congenital defects and viral myocarditis. This book should interest cardiologists, internists and students but should be of particular value to pediatric cardiologists.

ADVANCES IN CARDIOPULMONARY DISEASES Vol III Edited by Andrew L Banyai M D F C C P and Burgess L Gordon M D F C C P Chicago 1966 Year Book Medical Publishers Inc 348 pages Price $1 .50

This volume is a composite of 19 lectures from the 1963 series of postgraduate courses of the Council on Postgraduate Medicine Education of the American College of Chest Physicians. The papers include such subjects as compartments of lung volume and their physiologic significance, pirometry, respiratory acidosis, pulmonary edema, cystic fibrosis of the pancreas, metastatic tumors of the lung, auscultation, bedside diagnosis of arrhythmias and others. All papers are presented in the style of review lectures. This book should be of some interest to students and physicians. Those who read the journals regularly will find little if anything new in this series of lectures.

PROCEEDINGS OF THE NATIONAL STROKE CONGRESS Edited by Ralph E. DeForest, M.D. Springfield, Ill., 1966, Charles C Thomas. 234 pages. Price $7.50.

This is the proceedings of a congress sponsored by the American Heart Association, the American Medical Association, the Heart Disease Control Program of the United States Public Health Service, and the Vocational and Rehabilitation Administration of the United States Department of Health, Education and Welfare. The sessions were conducted in Chicago during October 1964. This summary of the presentation represents the contributions of many people. Sections of the book include discussions of the problem of strokes and their prevention, early care of the stroke patients, convalescence, and continuing care of the patient. There were meetings for the general public and a discussion of community programs. It is good to have the proceedings of such a meeting available for those who are interested, but it is unlikely that physicians in practice or students in general will find this book of much value. As is traditional for such meetings, little if anything new or unpublished was presented. Meetings of this sort probably are of value, although this point of view is debatable, especially in view of the fact that because so many similar meetings are held under so many different titles and circumstances, the material presented is always extremely repetitious.

## Books received

FOUR CONGENITAL CARDIAC DEFECTS. A STUDY OF THE PROFILE AND NATURAL HISTORY. American Heart Association Monograph No. 12, edited by James W. DuShane and William H. Weidman. New York, 1965, American Heart Association. 52 pages. Price $2.50.

YOUR WONDERFUL BABY. By Willis J. Potts. Chicago, 1966, Rand McNally & Co. 303 pages. Price $4.95.

# Announcements

Under the title of HYDRAULICS FROM THE MEDICAL POINT OF VIEW, the *Houille Blanche*, journal of the Société Hydrotechnique de France, is publishing in full the papers read at the first Symposium on Cardiovascular Assistance held in Paris on Nov. 18 and 19, 1965.

In the course of the symposium, which was attended by doctors, physiologists, cardiovascular surgeons, and specialists in fluid mechanics, such problems as the physiology of cardiac deficiency, arterial pulsations, counterpulsation, assistance techniques by-passing the left side of the heart, etc., were discussed.

Orders for this special number should be sent direct to the Houille Blanche, Boîte Postal 41, Grenoble, France.

The New York Academy of Sciences' CONFERENCE ON ATHEROSCLEROSIS: RECENT ADVANCES will be held at the Waldorf-Astoria Hotel, New York City, on Nov. 21-23, 1966. The Conference Chairman is Henry Haimovici, M.D., 862 Park Ave., New York, N. Y. 10021.

Invitations to attend the Conference may be obtained by writing to: Executive Director, The New York Academy of Sciences, 2 East 63rd St., New York, N. Y. 10021.

# Obituary

## Samuel Albert Levine

An inspired teacher has left us a pioneer in the diagnosis and treatment of heart disease The influence of Sam Levine on the lives of his contemporaries and of his host of students in this country and abroad promoted the new science of cardiology to take its place in the very forefront of all the specialties not only of internal medicine but also of surgery in both of which broader fields he kept an active interest all through his life But it was his vibrant spirit more than what he did and taught that appealed at once to all with whom he came in contact physicians patients and friends alike and will never be forgotten

Born in Poland Sam was brought to this country at the age of 3 years He was a brilliant scholar throughout his schooling while helping to earn his way through secondary schools Harvard College (A B 1911) and Harvard Medical School (M D 1914) by working as a newsboy which elevated the prestige of that job as street car conductor as waiter and as tutor

Trained at the Peter Bent Brigham Hospital where he was a long time disciple and friend of Henry Christian he became an eminent teacher at the Harvard Medical School where he achieved his professorship in 1948 as Clinical Professor of Medicine from which post he retired in 1957

He carried on postgraduate teaching in classes at the Brigham Hospital for over 30 years and many of the graduate students who took those courses are actively at work in cardiology all over this country and abroad today During the First World War he served with Thomas Lewis group at the Heart Hospital at Colchester in England with other American and British physicians He was pre-eminent in all three medical careers possible during the last generation namely practice teaching and research A professorship in cardiology was established in his name at Harvard University by a patient and former Dean C Sidney Burwell became its first incumbent



*Samuel Albert Levine 1891 1966*

Sam wrote several books particularly his pioneer monograph *Coronary Thrombosis Its Various Clinical Features* which appeared in the journal *Medicine* in 1929 After James Herrick who published hi

famous clinical introduction to coronary thrombosis in 1912 Sam was the next to recognize this disease This he did in a famous paper in 1918 based on two cases with differential diagnosis between acute cholecystitis and acute coronary thrombosis (*American Journal of the Medical Sciences* 155 57) Other books included his *Clinical Heart Disease* published in 1936 followed by four more editions and a later book entitled *Clinical Auscultation of the Heart* which appeared in 1949 written in collaboration with one of his most illustrious pupils Dr W Proctor Harvey of Georgetown University Many useful papers also came from his pen

His devoted family consisted of his wife Rosalind his son Herbert Chief of Cardiology at the New England Medical Center and two daughters Carol wife of Dr William B Schwartz eminent medical investigator also at the New England Medical Center and Joan wife of Simon Scheff attorney

Sam was a member of the leading medical and cardiological societies of this and foreign countries but most of all as I myself can testify after a companionship of 50 years Sam was an inspiration to us all

*Paul D White M D*
*Brookline Mass*

American Heart Journal

*September 1966 Volume 72 Number 3*

# Editorial

## The second sound in the pulmonary area

*Aubrey Leatham, F.R.C.P.**
*London, England*

Accurate analysis of the second heart sound is the first requirement for modern auscultation of the heart. It still does not seem to be generally appreciated by many practicing physicians that the second sound in the pulmonary area of normal subjects is composed of both aortic and pulmonary components; indeed, even in the pulmonary area aortic closure ($A_2$) is usually louder than pulmonary closure ($P_2$) and separation of the two components during the inspiratory phase of breathing is necessary before intelligent observations can be made about $A_2$ and $P_2$. Thus the common expression "$A_2$ is greater than $P_2$" when one is referring to areas has little significance and usually displays a remarkable ignorance of auscultation which became widespread between the First and Second World Wars. Potain[1] knew in 1866 that the second sound reduplicated during the inspiratory phase of continuous respiration. The mechanism of inspiratory splitting is of great interest and is due simply to the fact that the negative intrathoracic pressure of inspiration draws blood immediately into the right heart from its *extrathoracic* venous reservoir but not immediately into the left, since the negative pressure will influence all *intrathoracic* chambers and vessels equally and will thus have little or no *direct* effect on the flow of blood from pulmonary veins to left heart.[2] The increase in stroke volume of the right ventricle on inspiration results in prolongation of right ventricular systole and delay in $P_2$;[3] a few seconds later this increase in the volume of blood reaches the left heart and results in a slight increase in stroke volume of the left ventricle and delay in $A_2$,[4,5] although this is much less than on the right side since the change is damped by its passage through the lungs. During the inspiratory phase of continuous respiration at usual rates in normal subjects, $A_2$ is at its earliest when $P_2$ is at its latest, thus resulting in wide splitting of the second sound which may reach 0.1 second. In the expiratory phase, however, $A_2$ and $P_2$ are normally nearly fused, and clear separation persisting with slower deeper respiration is almost invariably abnormal, indicating that $A_2$ is early or, more commonly, that $P_2$ is late (e.g., right bundle branch block, left-to-right shunting, atrial septal defect increasing the stroke volume of the right ventricle, or pulmonary stenosis). $A_2$ may be late from prolongation of left ventricular systole (e.g., left bundle branch block or aortic stenosis) and will cause reversal of the order of valve closure in expiration. $P_2$ will precede $A_2$, usually

causing audible splitting which will (paradoxically) disappear during inspiration.[4,7]

More or less "fixed" splitting of the second sound occurs if the right ventricle is unable to vary its stroke volume, as happens with failure. If both $A_2$ and $P_2$ delay equally during inspiration (simultaneous prolongation of right and left ventricular systole) splitting of the second sound will also appear to be fixed. This usually indicates an interatrial communication, for inspiration here instantaneously increases the filling of both the right and left sides of the heart. It is a particularly obvious physical sign, since $A_2$ and $P_2$ are also clearly separated and easily heard because the ejection systolic murmur finishes before both components.

It has already been stressed that the second sound in the pulmonary area in normal subjects is composed of both aortic and pulmonary components. $P_2$ is much softer than $A_2$ and may be heard in the aortic area and at the lower left sternal edge but is not normally transmitted to the mitral area, where $A_2$ alone is heard. $P_2$ may be heard in the mitral area if accentuated from pulmonary hypertension or if the underlying ventricle is the right one, as in atrial septal defect, so that the presence of two components of the second sound in the mitral area is almost invariably abnormal.

Once $A_2$ and $P_2$ have been heard, other sounds in late systole and diastole can be identified and the timing of murmurs decided, and thus the second heart sound may well be considered to be the key to auscultation of the heart.[8]

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# Clinical communications

## Arrhythmias and potassium in man

*Alfred Pick, M.D.**
*Chicago, Ill.*

The purpose of this presentation is to review systematically and to illustrate the various disorders of cardiac rhythm induced by or related to abnormal levels of potassium as observed in clinical routine electrocardiography. Accordingly, the discussion will be limited to the analysis of *mechanisms* of arrhythmias without any attempt to correlate them with known bioelectric events at the cell membrane.[1] To this end it is feasible to separate fairly well the disorders of cardiac impulse formation and propagation under the effect of an excess of potassium on the one hand from those associated with a depletion of potassium on the other.

### Hyperkalemia

What unchecked and progressive hyperkalemia can do to the cardiac mechanism is illustrated in Fig. 1, which shows serial records from a 63 year old hypertensive and diabetic woman. A pre-existent pattern of left ventricular hypertrophy (Dec. 30, 1947) is on January 17 modified by uremic contour alterations—a prolonged Q-T interval and pointed T waves—while the sinus rhythm is unaffected. On the next day, as potassium toxicity develops, all signs of atrial activity have disappeared and a totally irregular ventricular action becomes progressively slower, eventually to cease with a preterminal monophasic deformation of the QRST. The origin of the preterminal ventricular irregular beats is unknown. However, recent studies in experimentally produced hyperkalemia using direct records from atria and ventricles[2] revealed that such beats can be related to continuous sinus impulses blocked from the bulk of the atrial myocardium but conveyed to the ventricles by some preferential path.

Although this type of sinoatrial block may come into operation in the human heart, it does not necessarily imply total cessation of atrial conduction. In Fig. 2 the ECG from an infant with tricuspid atresia who developed hyperkalemia acutely during a spell of severe hypoxia with apparent loss of the normal sinus mechanism, the atria do respond, although only intermittently, to impulses of a slowly escaping ectopic center located somewhere in or near the A-V junction. Such subsidiary supraventricular centers may be aroused by hypoxic hyperkalemia not only to slow but also to accelerated activity. When this takes place before the development of, or without, a sinoatrial block, the resulting arrhythmia is complete or incomplete A-V dissociation. A complex

From the Cardiovascular Institute and the Department of Cardiovascular Diseases, Division of Medicine, Michael Reese Hospital and Medical Center, Chicago, Ill.
Supported in part by Grant HE-041[illegible] from the National Heart Institute.
Presented at the Symposium on Potassium and the Heart, Oct. 1-2, 196[illegible], the University of Kentucky Medical Center, Lexington, Ky.
Received for publication Nov. 15, 196[illegible].
*Address: Cardiovascular Institute, Michael Reese Hospital and Medical Center, 29th Street and Ellis Ave., Chicago, Ill. 60616.




Fig. 1. Electrocardiographic effects of progressive hyperkalemia.

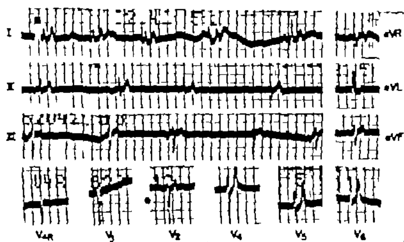



Fig. 2. Irregular escape of low atrial or A-V junctional pacemaker in hyperkalemia.

variety[4] of such a disorder is shown and diagrammatically analyzed in Fig. 3, which is the record from a 3½ month-old cyanotic infant who died after having been removed temporarily from its oxygen tent for recording of the electrocardiogram. The sinus rate has slowed to 50 while the junctional escape rate is speeded up to 75. This fortuitous numerical relationship between the rates of the two pacemakers having a common denominator of 25 results in a peculiar rhythm in which completely or partially conducted sinus impulses appear to be coupled to the ectopic ones. Thus, with continued complete ventricular capture, as in the upper panel, there is a so-called reversed ventricular bigeminy.[7] In the absence of captures, concealed penetration of the A-V junction by sinus impulses[8] is revealed by the constancy of the interectopic interval, as is indicated in the diagram in the lower panel.



Fig 3 Intra atrial first-degree A V and intra ventricular block with runs of ventricular tachycardia in advanced hyperkalemia

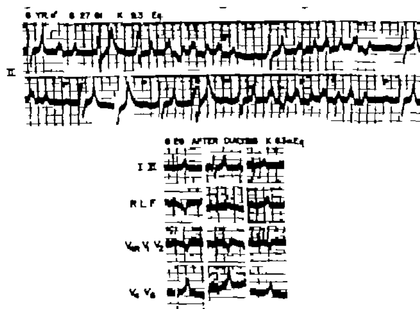


Fig 4 Incomplete A V dissociation with attempted and completed ventricular captures in hypox hyperkalemia

Enhancement of impulse formation by advanced hyperkalemia may also involve *ventricular* ectopic centers Fig 4 is a record from a 6 year old boy in whom acute renal failure and the associated electrolyte disorders have produced on *August 27* marked slowing of the atrial rate but only some of these presumably sinus impulses are conducted In most of the tracing there is A V dissociation due to runs of ventricular tachycardia and to single junctional premature beats The cause of this disturbance of rhythm is revealed by its disappearance on August 28 after partial correction of the hyperkalemia

A further remarkable feature of the record at the height of hyperkalemia is generalized slowing of impulse conduction it is revealed in the atria by the widening of the P waves to 0 24 sec in the ventricles by the QRS prolongation and peculiar shape of the supraventricular beats and in the A V junction by the prolongation of P-R to 0 40 sec The intraventricular conduction defect is discussed below (Fig 5 9) This record serves to illustrate that in clinical electrocardiography pure hyperkalemia even in its most advanced stages produces no more than a first degree A V block

When one is dealing with conduction disorders consequent to hyperkalemia some

consideration of the specific type of intraventricular block seems to be proper, although this does not fall strictly in the realm of cardiac arrhythmias. A classic example is illustrated in Fig. 5, which is the record from a 12-year-old boy with acute glomerulonephritis. Although leads of the frontal plane suggest a right bundle branch block, this is not borne out by the right precordial leads. The principal involvement of the terminal ventricular depolarization forces by the conduction disturbance has to be attributed to a severe diffuse but correctable peripheral conduction delay involving the free ventricular walls[4] rather than one or both of the main bundle branches.

If a more typical pattern of bundle branch block is found in hyperkalemic states, it can be related to the combination with predominantly unilateral ventricular pathology. Fig. 6 shows two records from an infant with transposition of the great vessels, mitral atresia, a diminutive left

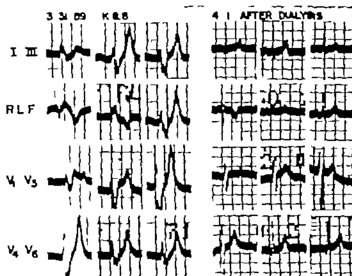



Fig. 5. The characteristic intraventricular block of severe hyperkalemia.

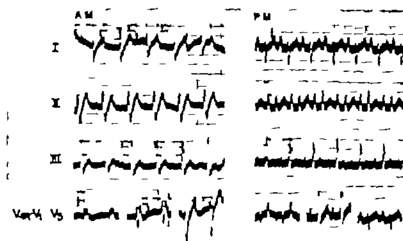



Fig. 6. Transient right bundle branch and mural block in hypoxic hyperkalemia.

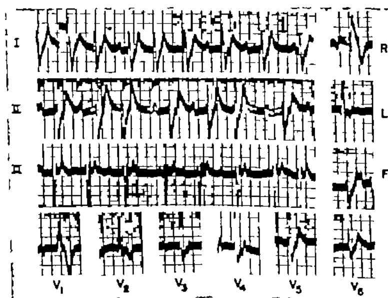



Fig 7 Atrial tachycardia with irregular A V conduction and right bundle branch and mural block due to hyperkalemia in acute cor pulmonale

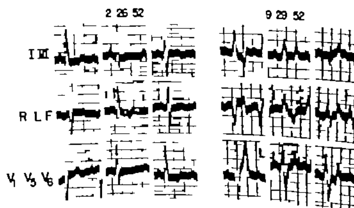



Fig 8 Left-sided intraventricular block in hyperkalemia

ventricle and pulmonic stenosis In the morning record (*A M*) taken during a hypoxic spell the typical right bundle branch block pattern appears associated with characteristic hyperkalemic contour alterations This pattern subsided in the afternoon (*P M*) to reveal the underlying right ventricular and atrial pathology A comparable but fatal event is seen in Fig 7 the record from a 30 year-old woman who developed extensive atelectasis and an acute cor pulmonale after hysterectomy A multifocal atrial tachycardia with irregular A V conduction and the intraventricular block involving the free myocardium as well as the right bundle branch can all be attributed to the combination of hypoxic hyperkalemia with acute dilatation of the right ventricle found at th autopsy

When hyperpotassemia develops n th presence of *left* ventricular patholog the mural block assumes the appearan d left bundle branch block as is illu in Fig 8 in the case of an man with hypertensive cardio

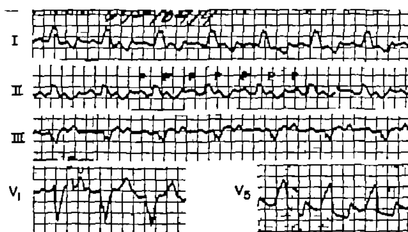



Fig. 9. Intraatrial, second-degree A-V, and left-sided intraventricular block in hypoxic hyperkalemia.

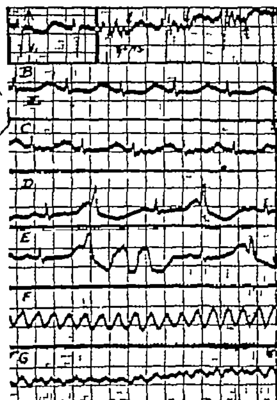



Fig. 10. Ventricular premature beats during the vulnerable phase in hypokalemia (19-year-old woman, K 2.5 mEq./L.). (From Lepeschkin and Rosenbaum: Coupling Interval of Ventricular Extrasystoles in Relation to the Heart Rate, the U Wave, and the Supernormal Phase of Excitability, Circulation 15:81, 1957, by permission of the American Heart Association, Inc. This record was interpreted according to the authors by Dr. Surawicz.)

case, and a serum potassium of 7.2 mg per cent on September 29. It can be noted that secondary ST-T alterations caused by the intraventricular conduction disturbance are modified but not cancelled by those due to hyperkalemia. Furthermore, it can be noted once again that A-V conduction is unaltered despite the high grade hyperkalemia. However, this may not be so in the case of hypoxic hyperkalemia. Fig. 9 shows the record from a premature infant in severe respiratory distress. Here the conduction disturbance is general, involving atria, ventricles, and the A-V junction, the latter in the form of a 2:1 A-V block.

The mechanisms involved in clinical arrhythmias caused by an excess of potassium are summarized in Table I.

## Hypokalemia

In contrast to the multiplicity of alterations in origin and propagation of the cardiac impulse which can be related to high levels of potassium in the blood, hypokalemia by itself only rarely produces such disorders.[3, 14] No such case was found in the electrocardiographic files of the Heart Station at Michael Reese Hospital, but an observation is on record, reproduced in Fig. 10, which shows the development of ventricular fibrillation from premature ventricular complexes occurring on top of large and prolonged T-U deflections—one of the several conditions revealing a vulnerable phase of the human heart.[15] However, in recent years ample experience has

Table 1 Mechanisms of clinical arrhythmias caused by an excess of potassium

| | Pacemaker activity | Impulse conduction |
|---|---|---|
| Primary | Slowed | Slowed +++ In the atria and ventricles<br>+ In the AV junction |
| Subsidiary | Enhanced in atria and ventricles | ++++ When associated with hypoxia |

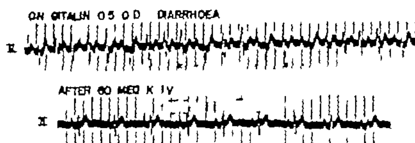



Fig. 11 Ectopic atrial tachycardia with irregular ventricular response caused by a relative excess of digitalis after depletion of potassium. In the upper panel the dots indicate conducted atrial impulses ... block ...

accumulated on the deleterious effects on the cardiac rhythm of a depletion of potassium in conjunction with digitalis medication.

The best known, perhaps because of the handy name that has been attached to it, is the so-called PAT with block, a typical example of which is shown in Fig. 11. In this 51-year-old man with chronic endobronchial disease, a condition in which this type of arrhythmia is particularly prone to occur, a maintenance dose of digitalis became excessive subsequent to an acute loss of potassium induced by diarrhea. The arrhythmia, which was promptly corrected by an infusion of potassium, was a rapid ectopic atrial rhythm with irregular ventricular response consisting of Wenckebach period with AV ratio varying between 3:2 and 4:3. In Fig. 12 the same type of arrhythmia is illustrated in 2 other digitalized patient. In one case (upper panel) the tachycardia with 3:2 ventricular response followed the loss of potassium caused by a recent diuresis. In the other case (lower panel) the atrial tachycardia with a persistent 3:2 AV conduction ratio developed when the hyperkalemia that followed bilateral adrenalec

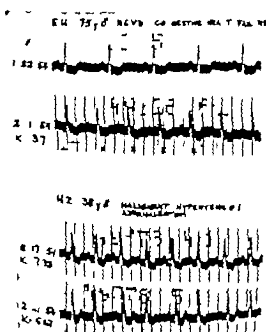



Fig. 12 Two examples of ectopic atrial ... with irregular ventricular response ... relative excess of digitalis ...

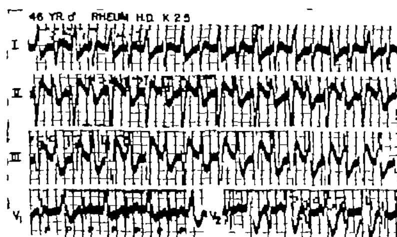



Fig. 16. Bidirectional tachycardia (with complete A-V dissociation) in hypokalemia.

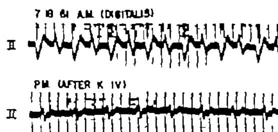



Fig. 17. Complete A-V dissociation in atrial fibrillation caused by nonparoxysmal A-V junctional tachycardia with bidirectional ventricular aberration before the infusion of potassium.

vanced hypokalemia could not be corrected and 2 hours later the patient died.

Yet patients with bidirectional tachycardia, although in grave danger, can be saved if the underlying depletion of potassium is recognized and treated in time (Fig. 17). This case of a 43 year old woman with mitral regurgitation and left bundle branch block also demonstrates that a regular bidirectional tachycardia induced by digitalis in the face of a depletion of potassium indeed originates in A-V junctional tissue,[1] for complete A-V dissociation is seen to persist after partial correction of the deficit in potassium with the atria fibrillating while the ventricles follow a supraventricular pacemaker at a less rapid rate.

Finally, the formation of *ventricular* ectopic impulses as a manifestation of digitalis toxicity may likewise become apparent after loss of potassium and respond promptly to the correction of the latter (Fig. 18). This 74 year old man with diffuse ischemic heart disease and old posteroinferior wall infarction developed bigeminy due to single ventricular premature beats which in Lead III multiplied to give rise to a run of bidirectional ventricular tachycardia. In contradistinction to the junctional type, it is here attributable to the multifocal formation of impulses in the ventricles because the intervals between the beats are not regular but alternate. However, this makes no difference with regard to the beneficial effect of the infusion of potassium.

Our experience concerning the mechanisms of clinical arrhythmias caused by a deficit in potassium are listed in Table II.

## Summary

The following conclusions from our observations in clinical electrocardiography

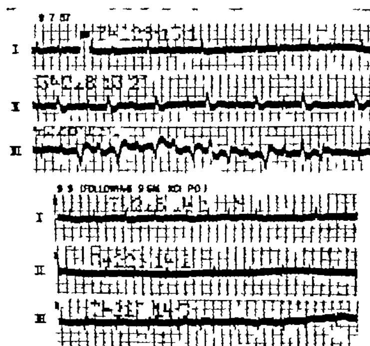



Fig. 13. Bidirectional ventricular tachycardia in atrial fibrillation caused by the formation of ventricular ectopic impulses and abolished by potassium medication.

*Table II. Mechanisms of clinical arrhythmias caused by a deficit in potassium*

| | | *Pacemaker activity* | *Impulse conduction* |
|---|---|---|---|
| Without digitalis | | Unchanged | Unchanged |
| With digitalis | Primary<br>Subsidiary | Unchanged<br>Enhanced in atria, A-V junction and ventricles | Unchanged (impairment caused by tachycardia and/or digitalis) |

can be drawn concerning mechanisms of potassium-induced arrhythmias.

1. Under the influence of *an excess of potassium* the formation of impulses becomes irregular with slowing of the primary pacemaker and acceleration of subsidiary centers. The conduction of impulses is slowed severely in ordinary atrial and ventricular myocardium but only moderately in the specific fibers unless it is aggravated by hypoxia or other associated pathology, especially acute ventricular dilatation.

2. *A deficit in potassium* by itself affects the formation and conduction of normal impulses only exceptionally. However, in digitalized patients the acute depletion of potassium induced by vomiting, diarrhea, diuresis, dialysis, or endocrine disorders causes an acceleration of the generation of ectopic impulses in the atria, in the A-V junction, and in the ventricles. Disorders of the conduction of impulses then occur in the A-V junction and ventricles but are only secondary because of the accelerated pacemaker rate or the digitalis medication.

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# Coronary arteriovenous fistula

## Nine operated cases

*Shigeru Sakakibara, M.D.**
*Masayoshi Yokoyama, M.D.*
*Atsuyoshi Takao, M.D.*
*Michio Nogi, M.D.*
*Haruto Gomi, M.D.*
*Tokyo, Japan*

The discovery of a continuous murmur at an unusual site over the precordium presents an interesting diagnostic problem. Coronary arteriovenous fistula is among the possible causes of such a finding. Coronary arteriovenous fistulas are divided into two major groups on functional grounds.[16] The first group includes anomalies without pulmonary or aortic valvular atresia, and the second group comprises coronary anomalies with pulmonary or aortic valvular atresia, characterized by retrograde coronary flow. Many differences in clinical signs and symptoms are observed between these two groups.

Nine operated cases belonging to the first group are reported here, and attention is drawn to the ease of diagnosis as well as surgical treatment.

### Case reports

Pertinent findings in the 9 cases from our Institute are shown in Table I.

*1. Clinical findings.* There were 5 female and 4 male patients. Subjective symptoms were lacking in all patients except one (Case 8). One patient, an 11 year old boy (Case 8), entered the hospital because of intermittent fever, general fatigue, purpura, and pain in the joints for 2 months prior to admission. Five patients (Cases 2, 4, 6, 8, and 9) had a history of recurrent respiratory infection. Systolic blood pressure was normal; however, diastolic blood pressure remained low, especially in 2 patients (Cases 5 and 8) in whom it was 0 mm. Hg when estimated by the auscultatory method. The chest film showed moderate to marked cardiomegaly in 6 patients. Peripheral pulmonary vascularity was increased in all except in one patient (Case 3). The aortic knob was prominent in only 2 patients. There were no specific findings in the electrocardiogram. Six patients showed left ventricular overloading. No electrocardiographic abnormalities were found in the others. All 9 patients showed sinus rhythm and a normal P-R interval. Only one patient (Case 2) had S-T depression in the left precordial leads.

The maximum continuous murmur was noticed in the pulmonary area in 2 patients (Cases 1 and 3). In 1958 one patient (Case 1) with a diagnosis of ventri

From the Heart Institute of Tokyo Women's Medical College, Tokyo, Japan.
Received for publication Nov. 17, 1968.
*Address: Heart Institute of Tokyo Women's Medical College, 10-Kawadacho, [illegible], Tokyo, Japan.

cular septal defect associated with pulmonary insufficiency underwent surgery the finding at operation was coronary arteriovenous fistula draining into the pulmonary artery In another patient (Case 3) the preoperative diagnosis was patent ductus arteriosus but since a continuous thrill remained over the pulmonary trunk even after ligation of the patent ductus the pericardium was opened and an anomalous coronary artery communicating with the pulmonary artery was found

*The location of the maximum continuous* murmur was noted along the left lower sternal border in 5 patients (Cases 2 4 5 6 and 8) Retrograde aortographs revealed an anomalous coronary artery draining into the right ventricle in these cases In 2 patients (Cases 7 and 9) in whom entry was into the right atrium the maximum point of the continuous murmur was at the second and third right intercostal spaces close to the sternum In all cases the intensity of the continuous murmur increased toward the second heart sound and then waned This probably was the reason that the pressure gradient between the aorta and the right cardiac chambers became much greater around the second heart sound In Case 9 of the present series a recording of the pressure in the fistula during the operation revealed the highest pressure around the second heart sound In this series no diastolic accentuation of the murmur was observed even by phonocardiography The continuous murmur became to and fro in character with systolic accentuation in Case 8 only this patient had a high right ventricular pressure 95 mm Hg in systole accompanied by bacterial endocarditis

*2 Diagnostic studies* The angiocardiogram was of great value not only in establishing the diagnosis but also in demonstrating anatomic details of the anomalous vessels We preferred to use selective retrograde aortography a procedure in which radiopaque material was injected into the base of the aorta through a catheter The aortograms clearly showed generalized dilatation and tortuosity of the coronary artery bearing the fistula By this method 7 cases were diagnosed correctly before operation (Fig 1)

Cardiac catheterization showed an oxygen step up in the chamber bearing the



Fig 1 Case 6 Anteroposterior (*left*) and right anterior oblique (*right*) positions The dilated coronary arteries drained into the right ventricle through the posterior wall of the heart

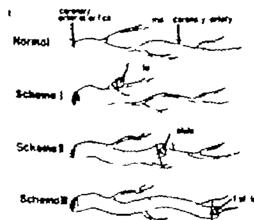



Fig. 2. Abnormal vessels were ligated at the sites indicated by the dotted lines. The right coronary artery, the left anterior descending coronary artery, and the left circumflex coronary artery were considered to be the main coronary vessel. *Schema I*: Fistula is found in one of branches of the vessel. *Schema II*: Fistula is observed at the middle part of the vessel. *Schema III*: Fistula is located at the end of the main artery.

fistula. The pulmonary arterial pressure was over 60 mm Hg in 3 patients (Cases 2, 5 and 8).

3. *Surgical procedure*. The abnormal vessel was invariably a part of a normally distributed coronary artery that had branches of normal size beyond the point of the fistula into the right side of the heart. Anomalous coronary arteries were classified into three types (Schemata I, II and III, Fig. 2).

Anomalous vessels were ligated as shown in Fig. 2. The operative procedure was concerned with division of the affected coronary artery as close as possible to the site of the fistula in order to insure that no collaterals entered below the site of division. In only one patient (Case 4, Schema III) were mattress sutures placed behind the coronary artery in a manner which would obliterate the fistulous communication without interruption of the continuity of the parent vessel. However, the continuous murmur reappeared approximately 1 month after operation and remained present for as long as 4 years afterward. In the other 8 patients in whom ligation of the abnormal coronary vessel was performed, the continuous murmur disappeared completely. During the operation electrocardiographic monitoring was important. Epicardial electrocardiography was considered to be the best way to observe the acute myocardial ischemia and its prompt abatement, because the electrocardiogram indicated the local ischemic changes of the myocardium after ligation of the fistula. Our experiences showed that even ligation of a small fistulous artery caused an elevation of the S-T segment in the territory supplied by the vessel. S-T elevations continued from a few minutes to about an hour. Most significant elevations of the S-T segment were noticed in cases belonging to Schema II (Cases 4 and 5) without any apparent effect on the color or contractility of the heart. Abnormal Q waves did not appear after surgery. All patients were operated upon without the use of extracorporeal circulation or hypothermia. No postoperative complications were noted, except for retrosternal abscess in Case 5.

#### Discussion

Apart from the consideration as to which coronary artery is involved, coronary arteriovenous fistulas are divided into five types according to the chamber or

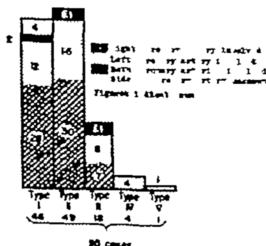



Fig. 3. Coronary arteriovenous fistulas without pulmonary or aortic valve atresia were classified into 5 types. Type I: Reference No. 2, 7, 9, 10, 14, 2 27, 29, 3 34, 40, 0. Type II: Ref. Nos. 1, 3, 10, 37, 33, 35, 49, 57, 59, 63, 68 1, 86. Type III: Ref. Nos. 4, 13, 1, 19, 25, 31, 59, 69, 0, 87, 85. Type IV: Ref. Nos. 26, 37, 39, 89. Type V: Ref. No. 90.

*Table I. Pertinent findings in 9 cases of coronary arteriovenous fistula*

| Case No. | Age (yr.) | Sex | Systolic thrill | Continuous murmur | Pulmonic second sound | X-ray findings: Aorta | X-ray findings: Pulm. conges-tion | X-ray findings: Heart thoracic ratio (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | 9 | M | − | gr. III 2nd LICS | + | Normal | + | 54 |
| 2 | 3 | F | − | gr. IV 4th LICS | ++ | Normal | ++ | 62 |
| 3 | 3 | F | + | gr. IV 2nd LICS | Normal | Normal | ± | 43 |
| 4 | 11 | F | Faint | gr. IV 3rd and 4th LICS | ++ | Small | ++ | 61 |
| 5 | 7 | F | Faint | gr. IV 4th and 5th LICS | + | Normal | + | 5[illegible] |
| 6 | 13 | M | + | gr. IV 3rd and 4th LICS | + | Normal | ++ | 58 |
| 7 | 5 | F | − | gr. III 2nd and 3rd RICS | Normal | Large | + | 50 |
| 8 | 11 | M | − | gr. III systolic gr. I diastolic 3rd LICS | ++ | Normal | ++ | 60 |
| 9 | 11 | M | − | gr. III 2nd and 3rd RICS | + | Large | + | 55 |

*LICS*: Left intercostal space. *RICS*: Right intercostal space. +: Condition present. −: Condition not present. *LVH*: Left vent[illegible]

vessel into which they drain (Fig. 3): *Type I*—draining into the right atrium. *Type II*—draining into the right ventricle. *Type III*—draining into the pulmonary artery. *Type IV*—draining into the left atrium. *Type V*—draining into the left ventricle.

Of the total of 118 reported cases of this anomaly which have been collected from the world literature, including 9 cases of our own, there were 49 of fistulous communication with the right ventricle and 46 of fistulous drainage into the right atrium. The right coronary artery is more frequently involved than the left. In 8 cases[illegible], including our Case 6, both coronary arteries participated in the fistula. The association of patent ductus arteriosus with coronary arteriovenous fistula has been documented in 5 cases[illegible], including our Case 3. In Fig. 3 we did not include the following papers: Jacobi's case[illegible] and Brown's case (these were considered to be cases of ruptured sinus of Valsalva), Gross's case[illegible] (the anomaly was not clearly described), and the last 3 of the 7 cases recently reported by Björk[illegible] (these were considered to be cases of atypical bronchial artery). It was difficult to differentiate coronary arteriovenous fistula of Type III from anomalous origin of the coronary artery or Bland-White-Garland syndrome. Murray's second case[illegible] and Michaud's third case[illegible] were considered to be instances of Bland-White-Garland syndrome.

When the fistula drains into the right atrium (Type I), the continuous murmur is best heard in the second and third right intercostal parasternal areas, or it is often clearly audible along the lower right or left sternal border (Fig. 4). When entry is into the right ventricle (Type II), the location of the maximum continuous murmur is noticed at the third, fourth, and fifth left intercostal spaces close to or over the sternum, and only in a few cases may it be noticed along the right sternal border. When the fistula is in communication with the pulmonary artery (Type III), the maximum point of the murmur is heard at the second or third left intercostal space. By auscultation it would be very difficult to differentiate this Type III from patent ductus arteriosus. There were 4 cases[illegible] in the literature in which the left coronary

| Electrocardiogram | | | Systemic blood pressure (mm Hg) | Coronary artery | Anatomic type |
|---|---|---|---|---|---|
| QRS axis | R wave in I (mv) | Interpretation | | | |
| +30 | 4 0 | LVH | 110/80 | Right | Type III Schema I |
| +9? | 4 4 | LVH | 110/40 | Left | Type II Schema III |
| +35 | 1 0 | Normal | 130/40 | Right | Type III Schema I |
| +80 | 4 7 | LVH | 120/70 | Right | Type II Schema II |
| +80 | 6 2 | LVH | 10?/0 | Right | Type II Schema II |
| +45 | 5 1 | LVH | 120/50 | Both | Type II Schema III |
| +85 | 3 2 | Normal | 100/40 | Right | Type I Schema I |
| +80 | 4 8 | LVH | 10?/0 | Right | Type II Schema III |
| +80 | 1 9 | Normal | 120/70 | Right | Type I Schema I |

hypertrophy

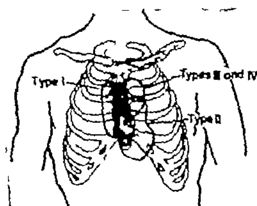



Fig. 4 The location of the maximum intensity of the murmur depends upon the site of the abnormal communication i.e. its position usually corresponds to the anatomic site of the chamber or vessel participating in the anomalous connection

artery drained into the left atrium (Type IV). In these cases the maximum continuous murmur was also noticed at the pulmonary area. However one case[10] with the fistula draining into the left ventricle was reported without description of the auscultatory findings

Certain conditions can cause a continuous murmur to be atypical such as pulmonary hypertension,[?] congestive heart failure,[?] atrial fibrillation[?] and low aortic diastolic pressure;[?] also a newborn baby[?] shows a soft systolic murmur instead of a continuous murmur

Gasul and associates[1] pointed out that dilatation of the aorta is common in this anomaly. However we consider that the aortic knob is usually more clearly noticeable in patent ductus arteriosus than in this anomaly. Intracardiac calcification was demonstrated in a case reported by Colbeck and Shaw.[?] There have also been reports of films showing unusual cardiac silhouettes due to aneurysmal dilatation of the coronary artery.[?] The dilated coronary artery *may* be seen as an excrescence on either border of the heart in posteroanterior chest films,[?] since the right coronary artery or the circumflex branch of the left coronary artery is most frequently involved

In 96 of 118 case reports there was electrocardiographic description and in 38 per cent of them (i.e. 36 of 96 cases) the electrocardiographic findings were nor-

mal. For 35 of the 46 Type I cases there was an electrocardiographic record. Only 5 of them showed right bundle branch block. In 6 of the 35 cases there was atrial fibrillation, and in all 6 cases the patient was over 60 years old.

Retrograde aortography helps in the differentiation of coronary arteriovenous fistula from many other anomalies which produce a continuous murmur over the precordium. This examination is easy to perform but necessary for the diagnosis of this anomaly and should be carried out from two projections in order to show the details of the involved coronary artery.

In infants the main cause of death is congestive heart failure[19] and pneumonia. However, beyond infancy congestive heart failure rarely develops, but bacterial endocarditis is more frequently experienced, as in Case 8.[illegible] Congestive heart failure becomes the main cause of death again after 40 or 50 years of age.[illegible] It is clear that patients with the Type I fistula easily develop atrial fibrillation which is often followed by congestive heart failure.[illegible] No advantage is to be gained by postponing operative intervention because asymptomatic lesions may eventually lead to bacterial endocarditis or cardiac decompensation.

Severe complications such as cardiac arrest[illegible] and cardiac failure[illegible] have been reported to follow the operation, but these accidents may not appear to be related to the ligation of the abnormal coronary artery itself. Patients included in Schemata I and III seem to be able to tolerate well the obliteration of the coronary artery. The patients belonging to Schema II suffer mostly from significant myocardial ischemia after operation. We consider, however, that there is usually enough adequate collateral circulation to allow for division of the affected coronary artery even in cases included in Schema II, as observed in our Cases 4 and 5. Thus the surgical technique of preserving the continuity of the abnormal artery instead of ligating it is usually unnecessary, although some authors have described successful procedures of obliteration of the fistulous communication without interruption of the continuity of the affected artery.

Some investigators insist that the main vessel should be ligated at its origin. However, dilated coronary arteries are not congenital in origin but are secondary to excessive blood flow, so that the ligation should take place at the site of connection to the chamber rather than at the origin of the vessel. Rupture of a dilated coronary artery after operation has not yet been reported. Surgical treatment with complete disappearance of many symptoms was carried out in Case 8 of our series; this patient had bacterial endocarditis and the highest right ventricular pressure of all reported cases. This case demonstrated clearly the effectiveness of surgical closure of the abnormal artery.

## Summary

Nine operated cases of coronary arteriovenous fistula were reported with a brief review of the literature. Retrograde aortography is the best diagnostic method, although a continuous murmur atypically located for patent ductus arteriosus is suggestive of this anomaly. In view of the relative simplicity of the operation, early correction should be made before severe complications appear.

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# The isoenzymes of lactic dehydrogenase

## I. Myocardial infarction and coronary insufficiency

*Donald O. Nutter, M.D.*
*Nelson P. Trujillo, M.D.*
*John M. Evans, M.D.**
*Washington, D. C.*

Lactic dehydrogenase (LDH) is present in man as five heterogeneous isoenzymes. Each isoenzyme molecule contains four subunits which are of two basic types, the "M" or muscle-liver unit and the "H" or heart unit.[1] $LDH_1$ and $LDH_5$ are homogeneous, containing four "M" and four "H" units, respectively, whereas $LDH_2$, $LDH_3$, and $LDH_4$ are combinations of the two basic subunits. The isoenzymes can be identified by differences in electrophoretic mobility, heat stability, and reaction rates with varied substrates and coenzymes.

Wroblewski and Gregory[2] have shown that heart muscle and erythrocytes contain large amounts of $LDH_1$. The LDH present in liver and skeletal muscles is largely $LDH_5$. $LDH_2$, $LDH_3$, and $LDH_4$ are distributed widely and in variable amounts in heart muscle, reticuloendothelial, lung, and other tissues. The five isoenzymes are present in the serum of normal human beings in the following relative concentration: $LDH_2 > LDH_1 > LDH_3 > LDH_4 > LDH_5$. The clinical applications of determining serum LDH isoenzyme activity are based on the assumption that this activity reflects, in part, the release of isoenzymes from tissues damaged by a specific disorder.[3]

A prospective study of LDH isoenzyme activity was conducted in patients with myocardial infarction, coronary insufficiency, pulmonary embolism, and a variety of other acute medical and surgical conditions. This paper presents the results in patients with acute myocardial infarction and acute coronary insufficiency.

### Material and methods

Thirty normal subjects (16 men and 14 women ranging in age from 21 to 61 years, mean age of 31 years) served as controls. Six other subjects were sampled daily for 5 days to determine individual variability in total LDH and isoenzymes. To test the reproducibility of the method, 20 determinations of total LDH were performed within 2 days on a single specimen of pooled human serum and on a single specimen from a patient with elevated serum total LDH.

Twenty-three patients (19 men and 4

From the Department of Medicine, George Washington University Hospital and School of Medicine, George Washington University, Washington, D. C.
Supported in part by Grant HE-[illegible] from National Heart Institute, National Institutes of Health, U. S. P. H. Service.
Received for publication Nov. 18, [illegible].
*Address: Director of Cardiology, George Washington University Hospital, [illegible] 23rd St., N.W., Washington, D. C. [illegible]

women) in whom the diagnosis of myocardial infarction was established by the history of acute substernal or precordial chest pain and confirmatory evidence of acute myocardial infarction in serial electrocardiograms (development of Q waves with appropriate changes in the S-T segment and T wave) were studied. Subjects in whom the clinical onset was indefinite were excluded.

Four of the 23 patients with myocardial infarction developed transient cardiac decompensation, 3 were hypotensive (clinical shock was present in one), 3 demonstrated a pericardial friction rub during the first postinfarction week, and all survived. All patients received Demerol or morphine for pain, and 18 were treated with a combination of heparin and Coumadin.

Eighteen patients with coronary insufficiency (13 men and 5 women) were studied. The diagnosis was made on the basis of typical substernal chest pain lasting more than 15 minutes and the appearance of acute myocardial ischemia in serial electrocardiograms. Subjects were excluded when other causes of chest pain were identified during the study.

Seven of the 18 patients with coronary insufficiency gave a history of previous myocardial infarction, whereas 5 others had experienced angina pectoris. Eight of the 18 experienced recurrent pain while under study, but none developed the abnormal Q waves of myocardial infarction in serial electrocardiograms. Two subjects developed transient cardiac decompensation, none were hypotensive, and all survived. Fifteen patients received Demerol or morphine and heparin and Coumadin.

In addition, serial determinations of enzyme activity before and during treatment with heparin and Coumadin were performed in 2 control patients without evidence of cardiac, pulmonary, or hepatic disease.

The serum activities of glutamic oxalacetic transaminase (SGOT), glutamic pyruvic transaminase (SGPT), total lactic dehydrogenase (LDH), and LDH isoenzymes 1, 2, 3, 4 combined, and 5 ($LDH_1$, $LDH_{2,3,4}$, $LDH_5$) were determined serially from the time of presentation (within 1 to 4 days of clinical onset) for 10 to 14 days. Samples of serum were frozen promptly, and the enzyme determinations were performed in duplicate within 3 days of collection. Hemolyzed sera were discarded. SGOT was determined by the method of Karmen and associates[4] and SGPT by the method of Wroblewski and LaDue.[5] Total LDH was determined by the spectrophotometric method of Wroblewski and LaDue.[6] LDH isoenzymes were separated by differences in heat stability, as described by Plagemann and associates[7] and determined by the technique used for total LDH.

Serial determinations (every third day or first 4 consecutive days) of bilirubin (method of Malloy and Evelyn[8]), alkaline phosphatase (method of Kline and associates[9]), and thymol turbidity (method of Shank and Hoagland[10]) were performed in all patients. Bromsulphalein (BSP) retention (method of Rosenthal and White[11]) was determined in a few cases.

### Results and comment

*Normal values.* The enzyme data obtained in control subjects are found in Table I. The LDH isoenzymes can be expressed as absolute units or as a percentage of total LDH activity. We have selected the former method to describe the results in this study.

Determinations of the coefficient of variation on the normal pooled serum and on the abnormal serum yielded a reproducibility of 5.6 and 2.3 per cent, respectively. Analyses of total LDH and LDH isoenzyme activities performed serially on control subjects showed a maximum daily variation of 60 units and a coefficient of variation for total LDH of 4.3 per cent, for $LDH_1$ of 5.9 per cent, for $LDH_{2,3,4}$ of 9.9 per cent, and for $LDH_5$ of 3.0 per cent. These daily variations in LDH activity do not significantly exceed the variations in the reproducibility of the method.

*Heparin and Coumadin controls.* The administration of these drugs in therapeutic dosage to the 2 control patients did not affect the serum activity of the enzymes. It was also noted that in the subjects with myocardial infarction and coronary insufficiency neither Demerol or morphine nor heparin or Coumadin seemed to influence the isoenzyme activities.

*Myocardial infarction.* The number of subjects, the mean values for each enzyme

Table I Values for serum enzyme activity from 30 normal control subjects

| | Mean | Standard deviation | Range (±2 S D ) | Per cent total LDH activity | Range per cent (± S D ) |
|---|---|---|---|---|---|
| SGOT | [illegible] | 8 5 | 10–44 | — | — |
| SGPT | 19 | 6 | 7 31 | — | — |
| Total LDH | 312 | 49 | 214–410 | — | — |
| LDH | 91 | 20 | 51 131 | 29 | 1 36 |
| LDH | 113 | 13 | 8 –139 | 36 | 28–44 |
| LDH | 10[illegible] | 15 | 77 137 | 35 | [illegible] 43 |

Table II Daily enzyme data from 23 patients with acute myocardial infarction

| | Day | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| SGOT | | | | | | | | | | | |
| Subjects | 8 | 16 | 22 | 22 | 23 | 2 | 2 | 22 | 18 | 16 | 12 |
| Abnormal | 5 | 13 | 17 | 14 | 9 | 6 | 7 | 7 | 3 | 2 | 1 |
| Normal | 3 | 6 | 5 | 8 | [illegible] | 15 | 15 | 15 | 15 | 14 | 11 |
| Mean (units) | 119 | 117 | 83 | 6[illegible] | 48 | 48 | 44 | 38 | 37 | 39 | 35 |
| SGPT | | | | | | | | | | | |
| Subjects | 8 | 16 | 22 | 2 | 23 | [illegible] | 22 | 22 | 18 | 16 | 12 |
| Abnormal | 4 | 5 | 8 | 5 | 3 | 5 | 5 | 4 | 3 | 1 | 1 |
| Normal | 4 | 11 | 14 | 17 | 20 | 17 | 17 | 18 | 15 | 15 | 11 |
| Mean | 35 | 35 | 31 | 30 | [illegible] | 30 | 27 | 3 | [illegible] | 20 | 15 |
| Total LDH | | | | | | | | | | | |
| Subjects | 8 | 18 | 2 | [illegible] | 23 | 2 | | 2 | 18 | 16 | 12 |
| Abnormal | 5 | 17 | [illegible] | 22 | 22 | 21 | 19 | 18 | 14 | 12 | 4 |
| Normal | 3 | 1 | 0 | 0 | 1 | 1 | 3 | 4 | 4 | 4 | 8 |
| Mean | 1 10 | 1 00 | 1 260 | 1 709 | 988 | 915 | 91 | 683 | 589 | 619 | 463 |
| LDH | | | | | | | | | | | |
| Subjects | 8 | 16 | [illegible] | 2 | 3 | 2 | 2 | 22 | 18 | 16 | [illegible] |
| Abnormal | 4 | 14 | 13 | 18 | 11 | 17 | 13 | 13 | 11 | 5 | 4 |
| Normal | 3 | 9 | 9 | 4 | 1 | 3 | 9 | 9 | 7 | 11 | 8 |
| Mean | 206 | 217 | 244 | 5 | 5 | 193 | 183 | 140 | 143 | 148 | 1 4 |
| LDH | | | | | | | | | | | |
| Subjects | 8 | 1 | 2 | 2 | 23 | 22 | 2 | [illegible] | 18 | 16 | [illegible] |
| Abnormal | 5 | 17 | 20 | 20 | 20 | 18 | 0 | 18 | 10 | [illegible] | 8 |
| Normal | 3 | 4 | [illegible] | 7 | 3 | 4 | | 4 | 8 | | 4 |
| Mean | 2[illegible] | 3 | 2 9 | 194 | [illegible] | 36 | [illegible] | 196 | 161 | 17 | 159 |
| LDH | | | | | | | | | | | |
| Subjects | 8 | 18 | 2 | [illegible] | 23 | [illegible] | 2 | 2 | 18 | 16 | 12 |
| Abnormal | 6 | 17 | 2 | | 2 | [illegible] | 1 | 21 | 17 | 15 | 10 |
| Normal | 3 | 1 | 0 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | |
| Mean | [illegible]17 | 679 | 691 | 66 | [illegible] | 487 | 390 | 350 | 288 | 376 | 230 |

The number of subjects sampled, the number with abnormal [illegible] subject [illegible] day 11

and the number of abnormal enzyme values for each day of the study are reported in Table II. The means of the serial enzyme curves for the subjects with myocardial infarction are illustrated in Fig. 1.

All 23 patients demonstrated an increase in total LDH, $LDH_1$, $LDH_{234}$, and $LDH_5$. In every case the maximal elevation occurred before the fifth postinfarction day and gradually declined without a secondary elevation. Twenty-one subjects demonstrated a considerably greater increase in $LDH_5$ than in $LDH_1$ or $LDH_{234}$, whereas in the other 2 subjects $LDH_5$ and $LDH_{234}$ increased in equal proportion.

The means of the various enzymes demonstrated the following: (1) Total LDH was elevated from day 1 to 11, with a peak value of 1,260 units on day 3. (2) $LDH_1$ was elevated from day 1 to 10, with a peak value of 275 units on day 5, and (3) $LDH_{234}$ and $LDH_5$ were elevated from day 1 to 11, with peak values on day 1 of 374 and 717 units, respectively. The

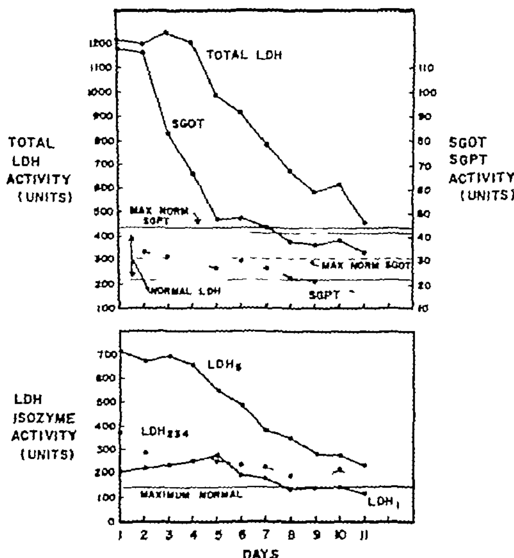



Fig. 1. The mean curves for SGOT, SGPT, total LDH, and the LDH isoenzymes 1, 234, and 5 from 23 patients with acute myocardial infarction are shown from the first to the eleventh postinfarction day. The normal range for total LDH activity and the upper limit of normal for SGOT, SGPT, and the LDH isoenzymes are included for reference.

maximal individual values were 3 300 units for total LDH 800 units for $LDH_1$ 940 units for $LDH_{2,3,4}$ and 1 760 units for $LDH_5$

SGOT was abnormal in 22 of the 23 patients An initial peak was observed before day 5 in every case however in 10 patients a late secondary elevation was also noted (mean peak on day 8) Three of the subjects with secondary elevations had experienced recurrent pain but in the other 7 there was no correlation with clinical events The secondary elevations in SGOT were not associated with a further rise in total LDH or LDH isoenzyme activity The group mean for SGOT was elevated on days 1 to 6 with a peak value of 119 units on day 1 The maximum individual value observed was 398 units

SGPT was abnormal in 13 patients (56 per cent) Peak values occurred before day 5 in 12 instances and 3 of these were associated with later secondary increases The remaining subject demonstrated a single abnormal elevation after the fifth day The group mean was elevated on days 1 and 2 with a maximum value of 35 units on day 1 The maximum individual value was 113 units

Only one of the 23 patients demonstrated significant and persistent abnormalities in liver function This patient had post necrotic cirrhosis confirmed by liver biopsy and although the LDH isoenzyme response to myocardial infarction was typical SGOT and SGPT values re

*Table III Daily enzyme data from 18 patients with acute coronary insufficiency**

| | Day 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| SGOT | | | | | | | | | | | |
| Subject | 13 | 15 | 16 | 16 | 16 | 15 | 15 | 13 | 10 | 9 | 7 |
| Abnormal | 3 | 7 | 1 | 0 | 3 | 3 | 2 | 1 | 4 | 1 | 1 |
| Normal | 10 | 13 | 15 | 16 | 13 | 12 | 13 | 12 | 6 | 8 | 6 |
| Mean (units) | 34 | 31 | 8 | 28 | 32 | 34 | 37 | 32 | 35 | 28 | 33 |
| SGPT | | | | | | | | | | | |
| Subjects | 13 | 15 | 16 | 16 | 15 | 14 | 14 | 12 | 10 | 9 | 7 |
| Abnormal | 2 | 2 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Normal | 11 | 13 | 15 | 15 | 15 | 14 | 14 | 12 | 10 | 9 | 7 |
| Mean | 24 | 3 | 20 | 18 | 17 | 18 | 18 | 16 | 17 | 16 | 15 |
| Total LDH | | | | | | | | | | | |
| Subjects | 13 | 15 | 16 | 16 | 16 | 15 | 15 | 13 | 10 | 9 | 7 |
| Abnormal | 4 | 7 | 4 | 3 | 2 | 2 | 4 | 1 | 3 | 2 | 1 |
| Normal | 9 | 8 | 12 | 13 | 14 | 13 | 11 | 12 | 7 | 7 | 6 |
| Mean | 401 | 479 | 384 | 354 | 367 | 391 | 389 | 375 | 416 | 391 | 360 |
| $LDH_1$ | | | | | | | | | | | |
| Subject | 13 | 15 | 16 | 16 | 16 | 15 | 15 | 13 | 10 | 9 | 7 |
| Abnormal | 7 | | 8 | 7 | 6 | 8 | 5 | 8 | 5 | 1 | 4 |
| Normal | 6 | 8 | 8 | 9 | 10 | 7 | 10 | 5 | 5 | 8 | 3 |
| Mean | 144 | 138 | 1 4 | 128 | 133 | 137 | 125 | 140 | 163 | 144 | 129 |
| $LDH_{2,3,4}$ | | | | | | | | | | | |
| Subjects | 13 | 15 | 16 | 16 | 16 | 15 | 15 | 13 | 10 | 9 | 7 |
| Abnormal | 6 | 9 | 6 | 5 | 8 | 9 | 9 | 5 | 4 | 3 | 2 |
| Normal | 7 | 6 | 10 | 11 | 9 | 6 | 6 | 8 | 6 | 6 | 5 |
| Mean | 120 | 139 | 126 | 115 | 120 | 140 | 139 | 112 | 1 4 | 137 | 1 2 |
| $LDH_5$ | | | | | | | | | | | |
| Subject | 13 | 15 | 16 | 16 | 16 | 15 | 15 | 13 | 10 | 9 | 7 |
| Abnormal | 6 | 4 | 5 | 4 | 3 | 3 | 5 | 3 | 2 | 2 | 1 |
| Normal | 7 | 11 | 11 | 12 | 13 | 12 | 10 | 10 | 8 | 7 | 6 |
| Mean | 123 | 140 | 139 | 111 | 11 | 120 | 121 | 113 | 125 | 113 | 106 |

*The number of subjects sampled [illegible] 18 subjects [illegible] coronary insufficiency [illegible]

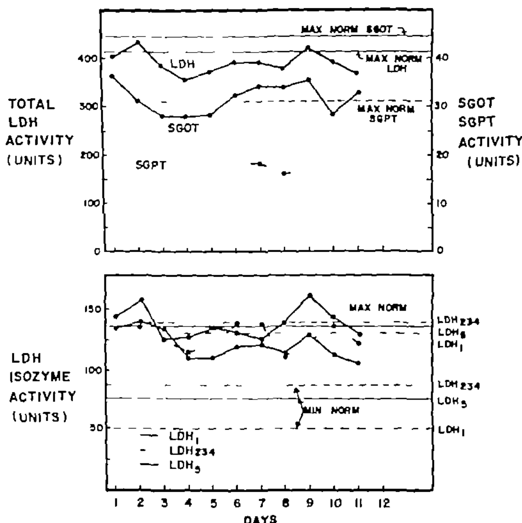



Fig. 2. The mean enzyme curves from 18 patients with acute coronary insufficiency are illustrated in the same manner as in Fig. 1.

remained elevated throughout the 11 days of study.

*Coronary insufficiency.* The daily number of subjects studied, mean enzyme values, and number of abnormal enzyme values are reported in Table III. The mean enzyme curves are presented in Fig. 2. Five of the 18 subjects had no abnormality in serum enzyme activity.

The mean of the total LDH values for all patients with coronary insufficiency was above normal only on days 2 and 9. The mean result of $LDH_1$ was slightly increased *throughout the period of study* with peaks on days 2 (158 units) and 9 (163 units). A minimal elevation to 140 units of the mean $LDH_{234}$ and $LDH_5$ occurred on days 6 and 2, respectively.

Total LDH was minimally elevated (mean peak of 560 units) in 11 patients (61 per cent). Six of these 11 subjects had peak elevations before day 5; of these, the predominant isoenzyme abnormality occurred in $LDH_5$ and $LDH_{234}$ in 3 cases, in $LDH_1$ in 2 cases, and equally in all isoenzyme fractions in 1 case. Total LDH in 3 of the 11 patients peaked after day 5, and the predominant isoenzyme abnormality occurred in $LDH_1$, $LDH_{234}$ plus $LDH_5$, and in all isoenzymes in 1 case each. *In the other 2 patients, early and* late elevations of total LDH activity were present and associated with elevation of $LDH_5$ in one patient and with elevations

of $LHD_1$ (early peak) and $LDH_{3,4}$ (late peak) in the other.

The mean SGOT curve in the subjects with coronary insufficiency remained normal. SGOT was modestly elevated (mean peak of 60 units) in 8 subjects (44 per cent). The increases in SGOT occurred before day 5 in 3 of the 11 subjects, after day 5 in 3, and both early and late in the other 2 subjects. The 10 SGOT elevations observed in 8 patients were associated in 5 with increased $LDH_{3,4}$ and $LDH_5$ activity, in 4 with increased $LDH_1$ activity, and in 1 with normal isoenzyme activity.

Four of the late SGOT peaks described were associated with recurrent chest pain. The findings in 2 patients with associated SGOT and LDH isoenzyme abnormalities are illustrated in Figs. 3 and 4.

A modest abnormality in SGPT activity was observed in 3 cases (17 per cent), while the mean curve for SGPT remained normal. The observed elevations peaked before day 5 and accompanied SGOT elevations.

Significant or persistent abnormalities in liver function were not observed in these patients.

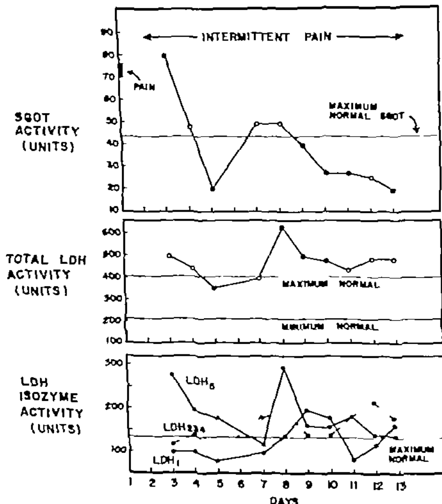



Fig. 3. The daily enzyme activities are shown in a 33 year-old woman (E.S. No. 42536) with angina pectoris of 1 month duration, acute coronary insufficiency occurring 3 days before enzyme studies, and intermittent anginal pain occurring during the period of observation. This subject illustrates modest SGOT and total LDH elevations associated with elevated LDH suggesting the presence of myocardial necrosis.

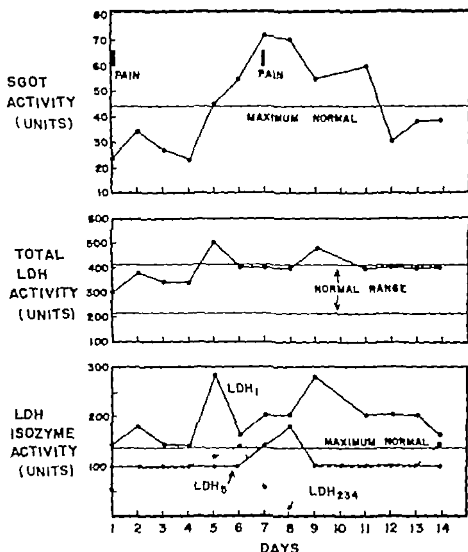



Fig 4 The enzyme curves from a 59 year-old man (H S No 3 33189) with a history of angina pectoris of 2 years duration acute coronary insufficiency occurring at onset of enzyme studies and recurrent coronary insufficiency on the seventh day of observation The association of SGOT and total LDH elevations with abnormal $LDH_1$ activity is demonstrated in this case

## Discussion

*Myocardial infarction* The serum activities of total LDH and SGOT may be increased in a variety of situations such as myocardial infarction chronic congestive heart failure hepatobiliary disease musculoskeletal diseases certain neoplasms and a number of hematological disorders The isoenzymes of LDH have been helpful in differentiating myocardial infarction from many of the conditions noted above Wroblewski and associates[12] have described increased activity of $LDH_1$ and $LDH_2$ in transmural infarction This increased activity occurred earlier than that seen in SGOT and in total LDH persisted for a number of days after SGOT and total LDH activity had returned to normal and was present in cases of subendocardial infarction in which SGOT and total LDH were normal Several investigators[13,17] have confirmed the abnormalities of $LDH_1$ in myocardial infarction and have commented upon the reliability of the LDH isoenzymes in distinguishing myocardial infarction from other cardiovascular diseases hepatobiliary disease and the post operative state

The present study of uncomplicated myocardial infarction confirms the pattern of SGOT and total LDH activity described in previous investigations. The $LDH_5$ response in our cases was immediate, significant (the mean was 6 times normal at maximum), and prolonged. The degree and duration of this response supports Wroblewski's concept that necrosis alone does not account for the enzyme activity observed.[18] We have noted abnormalities of $LDH_5$ activity occurring both in the presence of normal total LDH and for a considerable time after total LDH has returned to normal.

Also of interest are the absolute elevations of $LDH_{234}$ and $LDH_1$ in these subjects. The activity of $LDH_{234}$ closely parallels that of $LDH_5$ and may well reflect the release of myocardial $LDH_4$. The increased $LDH_1$, however, peaked on the fifth day and may reflect increased hepatic activity, since little $LDH_1$ is present in heart muscle. An increase in hepatic enzyme activity (aldolase, SGOT, and LDH) has been described as a non-specific reaction to acute stress situations (exclusive of shock and cardiac or liver disease).[11] The results of periodic hepatic function tests in our cases do not support acute hepatocellular dysfunction as a cause of increased $LDH_1$ activity, although the more sensitive tests, such as urine urobilinogen or BSP excretion, were performed infrequently. In an earlier study from this clinic, urobilinogen was found to be elevated frequently in patients with acute myocardial infarction.[20]

*Coronary insufficiency.* Experimental coronary insufficiency in the dog was not associated with increased SGOT activity unless myocardial necrosis occurred.[21] A review of the SGOT test in angina pectoris and coronary insufficiency supports this concept.[22] These reports and a subsequent review by Resnik[23] describe patients with coronary insufficiency, nonspecific changes in the electrocardiogram, and abnormal SGOT activity implying the presence of infarction. A number of these cases reported in the literature have demonstrated either late or combined early and late elevation of SGOT activity similar to that seen in 5 of 18 cases in the present study. There is reason to believe that some of these alterations in SGOT activity are hepatic and not myocardial in origin. We are not aware of previous studies of LDH isoenzyme activity or of consistent elevation of total LDH in coronary insufficiency.

The modest increases in total serum LDH observed in 11 of our 18 patients with coronary insufficiency occurred both early (less than 5 days) and late in relation to the onset of chest pain. The associated elevation of $LDH_{234}$ and $LDH_5$ in 6 of 11 subjects (both with early and late peaks) suggests myocardial necrosis. The elevation of $LDH_1$ activity in 6 of these same 11 patients and the borderline elevation of the mean $LDH_1$ for the group with coronary insufficiency as a whole may reflect increased hepatic enzyme release as discussed above. The 5 elevations of SGOT occurring early and late in association with the increases in $LDH_{234}$ and $LDH_5$ described above may also suggest infarction. It appears that SGOT, total LDH, and LDH isoenzyme abnormalities are inconstant in acute coronary insufficiency and, when present, reflect myocardial necrosis in only approximately 50 per cent of cases if $LDH_5$ is a reliable index of necrosis.

## Summary

In a prospective study, the serum activities of SGOT, SGPT, total LDH, and the LDH isoenzymes 1, 234 combined, and 5 were determined serially in 23 patients with acute myocardial infarction and 18 patients with acute coronary insufficiency.

In all of the 23 subjects with myocardial infarction, there was a prompt, marked, and persistent elevation in serum activity of heart muscle lactic dehydrogenase ($LDH_5$) accompanied by a significant but less marked elevation of $LDH_{234}$ and $LDH_1$. Certain features of these changes are characterized and the associated SGOT and SGPT abnormalities are discussed.

The incidence and nature of the enzyme abnormalities occurring in 18 subjects with acute coronary insufficiency are discussed. If $LDH_5$ is a reliable criterion, the isoenzyme results suggest that only 50 per cent of the observed elevations in

SGOT and total LDH activity are associated with myocardial necrosis

Our study confirms the value of the serial analysis of LDH as a sensitive and more specific aid in the diagnosis of acute myocardial infarction This test also will be of particular value in patients who present several days after clinical onset

We would like to thank Mrs Donald H Lareau Jr for her valuable technical assistance

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# Late systolic murmurs, clicks, and whoops arising from the mitral valve

## A transseptal intracardiac phonocardiographic analysis

*Donald F. Leon, M.D.*
*James J. Leonard, M.D.***
*Frank W. Kroetz, M.D.****
*William L. Page, M.D.*
*James A. Shaver, M.D.*****
*John F. Lancaster, M.D.******
*Pittsburgh, Pa.*

The acoustical events which characterize the usual case of mitral insufficiency have been clearly defined. In most instances, the murmur is high pitched, pansystolic, best heard at the apex, and radiates toward the left axilla and left subscapular areas. Ventricular gallop rhythm, a short diastolic flow rumble, and wide splitting of the second heart sound are observed in a significant number of cases of advanced mitral incompetence. The acoustical events associated with mitral stenosis are even better defined. These include accentuation of the first heart sound, the mitral opening snap, and the characteristic long diastolic murmur.

In the past, late systolic murmurs were thought to arise from the extracardiac areas.[1] The incidence of a history of pleural and pericardial disease was found to be high in patients with late systolic murmurs as well as in those who had systolic clicks or systolic gallops.[2,3] The infrequently observed variety of musical murmur referred to as a "systolic whoop" by Levine and Harvey[4] and McKusick[1] in their respective texts has been attributed for the most part to epicardial sources and occasionally to intracardiac sources. This type of murmur has also been euphonistically referred to as a "honk."

Recently, a number of patients with late apical systolic murmurs have been demon-

From the Department of Medicine, Division of Cardiology, University of Pittsburgh School of Medicine, Pittsburgh, Pa.
This work was supported in part by Grant No. HE 08473-02 from the National Heart Institute, United States Public Health Service, and Grant No. F30 [illegible] Health Research and Services Foundation, Pittsburgh, Pa.
Received for publication Dec. 8, 1964.
*Instructor, Medicine, Division of Cardiology, University of Pittsburgh School of Medicine. [illegible] Research Fellow in Cardiology, Lebanon County Heart Association of the Pennsylvania Heart Association.
**Associate Professor of Medicine and Director of the Division of Cardiology, University of Pittsburgh School of Medicine.
***Associate Professor of Medicine, Division of Cardiology, University of Pittsburgh School of Medicine.
****Instructor in Medicine, Division of Cardiology, University of Pittsburgh School of Medicine. Formerly Postdoctoral Trainee supported in part by Grant No. HTS-5467-C3 from the National Heart Institute, United States Public Health Service.
*****Postdoctoral Fellow supported by Grant No. 5 F HE 20,370-0[illegible] from the National Heart Institute, United States Public Health Service.

strated to have mild mitral insufficiency.[3,4] The response of this type of murmur to the infusion of vasopressor and the inhalation of amyl nitrite has also been discussed.[6] The relationship between bulging mitral leaflets, angiographic evidence of late systolic mitral regurgitation, and the late systolic murmur recorded retrograde in the left ventricular inflow tract has been studied in some detail.[7,8]

It is the purpose of this report, first of all, to define the regurgitant nature of the late systolic murmur by localizing the murmur to the mitral regurgitant pathway within the left atrium and by recording its generation across the mitral valve; second, to demonstrate that systolic clicks and systolic whoops do, in fact, at times arise from the mitral valve and its supporting structures; and third, to demonstrate the auscultatory continuum of mitral insufficiency.

## Materials and methods

Nine patients were selected for this study on the basis of the chest wall phonocardiographic demonstration of those acoustical events under consideration, namely, late systolic murmurs, systolic clicks, and systolic whoops. Mitral insufficiency, when present, was documented by localization of a murmur to the mitral regurgitant pathway, irrespective of the duration of the murmur, by selective left ventricular angiographs, by surgical inspection, and by autopsy examination. Mitral stenosis was documented by simultaneous recordings of transvalvular pressure gradients at cardiac catheterization and by surgical inspection.

One of the patients in this study had neither mitral insufficiency nor stenosis, even though the acoustical events in question were found to arise from the mitral apparatus.

Each patient was hospitalized, and, in addition to complete clinical evaluation, electrocardiogram, and cardiac roentgenographic series, a chest wall phonocardiogram was recorded. These recordings were made on a polybeam recorder,* with the use of a contact barium titanate microphone* and an air conduction crystal microphone.† The carotid pulse contour was recorded indirectly by means of strain gauges.‡

All patients underwent right heart catheterization and transseptal left heart catheterization with the recording of intracardiac sound and pressure by means of a modification of the Ross technique described previously.[9,10]

This technique involves the introduction of a No. 9F Ross catheter transseptally over a 16 gauge Ross needle and its subsequent manipulation into the left ventricular cavity.[11] The needle is then withdrawn and a barium titanate phonocatheter§ is introduced through the Ross catheter until its transducer extends slightly beyond the tip of the Ross catheter (Fig. 1). Sufficient unoccluded lumen remains between the phonocatheter and the Ross catheter to permit the recording of pressure tracings of good frequency response. The only modification required in the Ross catheter is that it have a 2.0 or 2.5 cm. Brockenbrough type of bend on its tip to facilitate manipulation into the left ventricular cavity.[12]

Simultaneous chest wall phonocardiograms were obtained in each case. Cineangiocardiograms‖ were recorded after injection into the left ventricle in 6 cases, and a biplane¶ angiocardiogram was recorded after injection into the left ventricle in 1 case.

The mitral valve was inspected at operation during cardiopulmonary bypass in 2 cases, and autopsy examination was performed in 2 cases.

## Description of cases and results

At the time of transseptal intracardiac phonocardiographic study, 5 patients who had clinically audible late systolic murmurs were found to have late systolic murmurs when recordings were made directly

*DR8 Research Recorder, Electronics for Medicine, White Plains, N. Y.

†[illegible] Electronics for Medicine, White Plains, N. Y.

‡[illegible] Electronics for Medicine, White Plains, N. Y.

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§[illegible] Electronics Laboratory, [illegible]

‖Modified Arriflex camera (35 mm.), [illegible] Corporation, [illegible] Station, N. Y. [illegible] Corporation, [illegible] White Plains, N. Y.

¶Elema Schonander, [illegible], N. Y. Company, [illegible]



Fig 1 A No 9F Ross transeptal catheter with a specially curved tip crossing the mitral valve and No 5F phonocatheter passing through its lumen and extending 1 cm beyond the tip of the Ross catheter The pressure-conducting lumen can be seen between the phonocatheter and the Ross catheter

in the regurgitant pathway above the mitral orifice These patients may be distinguished from those who have pansystolic murmurs with late systolic accentuation in the left atrium but in whom only the late systolic vibrations are audible on the chest wall The former group usually demonstrates only late systolic regurgitation by angiography whereas the latter group has pansystolic regurgitation The former group tends to have small regurgitant volumes which is not necessarily the case in the latter group

In each case of intracardiac late systolic murmur as the sound pressure recording apparatus was withdrawn from the body of the left ventricle into the atrium the murmur was first recordable just below the mitral valve At the level of the valve itself which was determined by atrialization of the ventricular pressure contour there was a distinct increase in intensity of the murmur With further pullback into the body of the atrium the intensity of the murmur again diminished until it was not recordable near the septum or in the atrial appendage These observations would appear to define the precise origin of the murmur at the mitral orifice and lend further support to the already weighty evidence that this type of murmur is a regurgitant phenomenon [4 8]

*Case 1* which is representative of the group of murmurs under consideration was that of a 61 year old woman without historical evidence of rheumatic fever but with a documented history of thyroid carcinoma with pulmonary metastases and malignant cells in the pleural fluid She had been treated with radioactive iodine 3 years prior to study and there was no evidence of recurrence of the pulmonary lesions At the time of cardiac investigation a carboangiocardiogram revealed pericardial thickening

The murmur recorded in the left atrium is the typical systolic murmur of late mitral insufficiency (Fig 2) After the first heart sound there is a short period in which no murmur is seen Thereafter a high pitched crescendo murmur with instances of fast activity peaks near the second sound and then rapidly terminates just after the sound of aortic valve closure The continuance of the murmur beyond the aortic second sound is due to the time interval which occurs while the ventricular pressure is dropping from the aortic diastolic level to the level of left atrial pressure

There is very little doubt that not too long ago this murmur would have been considered to be of extracardiac origin particularly in view of the history of pulmonary pleural and pericardial disease Certainly the relationship between this type of murmur and pleuritis and pericarditis in the past is of more than circumstantial interest There might well be a cause and-effect relationship as yet undiscovered

*Case 2* is that of a 34 year old woman who had experienced repeated episodes of rheumatic fever and recent hyperthyroidism Although she was asymptomatic a systolic murmur and click were present Directly above the mitral valve there were a few soft murmur vibrations in early systole and a mid systolic click introducing a loud late systolic murmur As the microphone was moved away from the valve the early systolic components

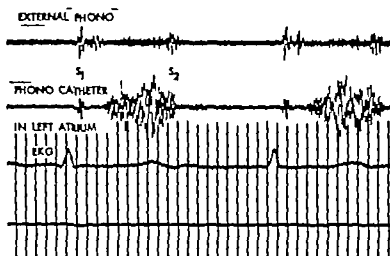



Fig. 2. The late systolic murmur of mitral insufficiency recorded in the left atrium in a patient with pericardial thickening and a history of thyroid malignancy involving the lung and pleural space. A definite clear area is noted between the first sound ($S_1$) and the onset of the murmur in the left atrium. The murmur envelops the second sound ($S_2$). The ejection sound which follows $S_1$ on the external phonocardiogram is not recorded in the left atrium.

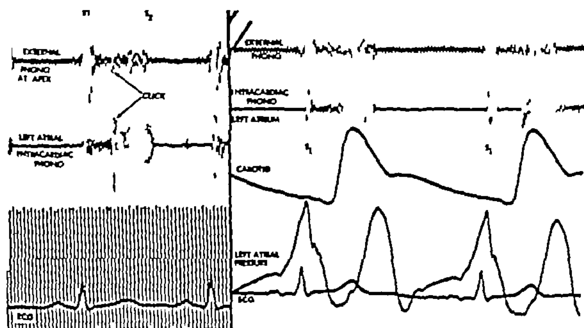



Fig. 3. A 44-year-old woman with a history of rheumatic fever and documented incompetence of the posterior mitral leaflet. The external apical phonocardiogram demonstrates a pansystolic murmur with late systolic accentuation. The late accentuation is introduced by a click. The murmur including the late accentuation and systolic click is localized to the mitral valve orifice by the intracardiac phonocatheter (*left panel*). *In the right panel* two complexes are seen. The first is recorded closer to the mitral valve and the second farther back from the orifice. As the microphone is withdrawn from the mitral orifice the early components of the murmur disappear completely whereas the click and late systolic murmur are preserved. *The a, c, and v waves* of the left atrial pressure pulse are clearly identified.

of the murmur disappeared (Fig 3) This phenomenon has been repeatedly observed in the past [9]

The time interval between the first sound and the click which introduces the murmur varied from beat to beat Selective left ventricular cineangiocardiographic study revealed regurgitation limited to the posterior mitral leaflet It was not possible to determine whether the incompetent leaflet was prolapsed However the intra atrial phonocardiogram displays the type of murmur and click reported in cases of prolapse of the leaflets [7]

*Case 3* is that of a 26 year old woman who had experienced rheumatic fever as a child She was asymptomatic when a murmur was recently detected Phonocardiographic recordings demonstrated a late systolic regurgitant murmur introduced by a click Transseptal phonocardiograms showed this click and murmur to be arising from the mitral orifice The cineangiocardiogram revealed minimal mitral regurgitation and all other hemodynamic data were normal

*Case 4* is that of a 39 year old man who was known to have a heart murmur at the age of 16 years and whose first electrocardiogram at that time revealed right bundle branch block There was no history of rheumatic fever and the patient's exercise tolerance had remained normal Fig 4 shows the late systolic murmur recorded in the left atrium in association with right bundle branch block Mild mitral regurgitation was documented by biplane angiocardiography

Right bundle branch block is shown delaying the sound of pulmonary valve closure and the sound of aortic valve closure is in the terminal vibrations of the murmur Thus the murmur of late mitral insufficiency in the presence of delayed pulmonary valve closure might at first be mistaken for an ejection murmur

This murmur when recorded above the mitral orifice has many late vibrations of such high frequency that they exceed the limits of the recorder in the same fashion as do the vibrations of the phenomenon known as systolic whoop (see Fig 7)

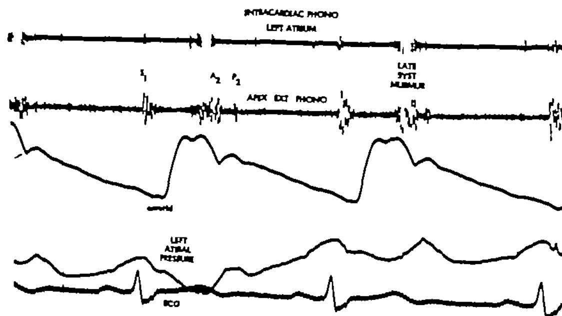



Fig 4 The late systolic murmur of mitral insufficiency recorded in the left atrium of a 39 year old man The delay of pulmonary valve closure ($P_2$) related to right bundle branch block (*ECG*) is [illegible] the normal left atrial pressure (a and v) The regurgitant murmur extends up to aortic valve closure ($A_2$) identified by the incisura of the indirect carotid pulse

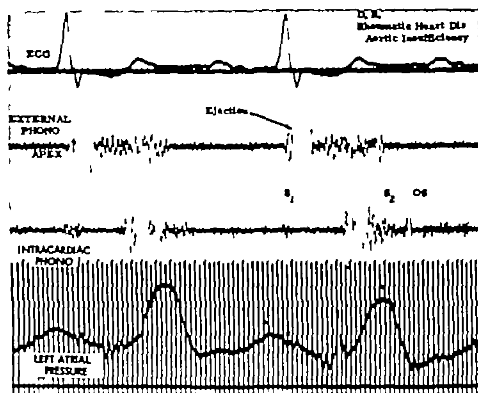



Fig 5 A 54 year-old man with the late systolic murmur of mild mitral insufficiency related to left ventricular hypertrophy and dilation and dominance of the anterior cusp The earlier ejection murmur can be seen to blend with the late systolic murmur to occupy all of systole in the external phonocardiogram The late systolic regurgitant murmur and an opening snap (*OS*) in the absence of mitral stenosis are recorded in the left atrium

*Case 5* is that of a 54 year old man with clear clinical and angiographic evidence of rheumatic aortic insufficiency A mitral regurgitant systolic murmur was easily heard at the apex by every observer and it was thought by all except one to be pansystolic This single observer maintained that the early vibrations heard at the bedside were referred to the apex from the aortic ejection murmur and that the apical murmur was limited to the latter part of systole Simultaneous left atrial sound pressure recordings definitely established the presence of late systolic regurgitation with normal atrial pressure whereas the external phonocardiogram recorded the additional early ejection murmur (Fig 5) A mitral opening snap was repeatedly recorded near the mitral valve in this patient in whom there was no mitral stenosis Selective left ventricular cineangiography demonstrated minimal regurgitant opacification of the left atrium At the time of operation for aortic insufficiency a mitral regurgitant jet could not be felt when the left atrium was invaginated The mitral valve was not visually inspected at operation The patient died postoperatively and autopsy revealed a jet lesion on the posterior wall of the left atrium thus indicating that some mitral regurgitation had been present The posterior mitral leaflet was of normal thickness and both sets of chordae tendineae were normal The anterior mitral leaflet was considerably larger than the posterior leaflet It had become slightly thickened by the aortic regurgitant jet Closure was accomplished by the dominant anterior leaflet covering some of the area usually covered by posterior leaflet substance The left ventricle including the papillary muscles was dilated and hypertrophied The mechanism of mitral regurgitation appeared to be that the dilated and hypertrophied left ventricle

coupled with the hypertrophied papillary muscles held the small posterior leaflet deeper in the ventricular cavity than usual during systolic contraction, thus permitting the larger anterior leaflet to slip by the edge of the posterior leaflet as ventricular volume decreased during late ventricular ejection. Thus, late systolic mitral insufficiency was found to be related to ventricular hypertrophy and cusp dominance in the absence of rheumatic distortion of the mitral valve.

*Case 6* is that of a 44 year old woman with surgically documented rheumatic mitral valve disease. She previously had undergone two mitral commissurotomies and was suffering again from a recurrence of symptoms. Clinical evaluation and catheterization indicated the presence of predominant mitral stenosis with some mitral insufficiency and pulmonary hypertension. A systolic regurgitant murmur occurring early in systole and ending with a mid systolic click was audible and recordable externally. The intracardiac microphone (Fig. 6) recorded the click in the left atrium in the region of the mitral valve. The patient underwent surgical excision of the mitral valve and its supporting structure, and a mitral prosthetic valve was installed. Postoperatively, the click was no longer present. Thus, in a patient with two previous episodes of pleuritis and pericarditis, each surgically induced, the systolic click appears to have originated at the mitral valve rather than arising from the pericardial surface.

Furthermore, this case might well complete the spectrum of timing of mitral regurgitant murmurs in that the murmur was limited to early systole and was terminated by a click. This circumstance may be explained by a surgically induced valvular deformity in which regurgitation would

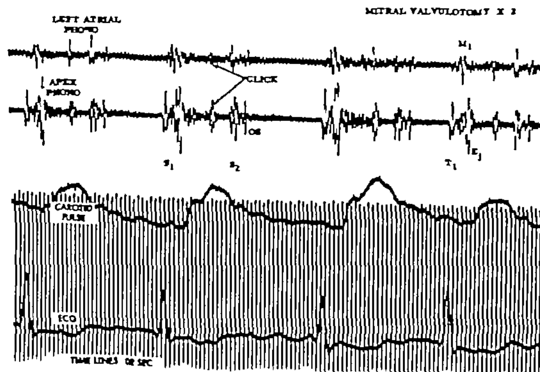
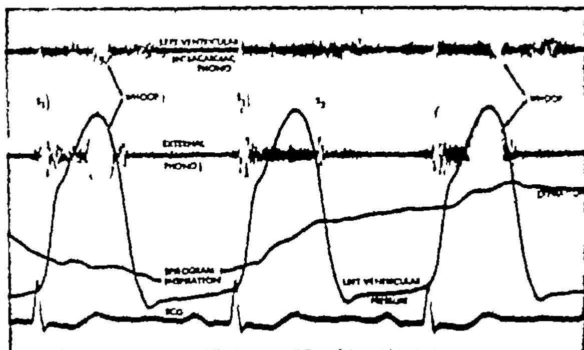



Fig. 6. A 44 year-old woman with recurrent mitral stenosis in whom a systolic click was identified in the apex phonocardiogram. The intracardiac microphone would record this click only over the mitral orifice. The click can be seen to terminate an early regurgitant murmur. Tricuspid ($T$) and mitral ($M$) components of the first sound and a pulmonary ejection sound ($E_j$) are identified, as well as the second sound ($S$) and opening snap ($OS$).




[illegible]

continue until another checkin movement represented by the click would permit the valve to be competent.

Several additional points about this case are of interest. The first sound on the external phonocardiogram occurs 0.04 sec. after the Q wave and thus represents the tricuspid first sound accentuated by pulmonary and right ventricular hypertension. The mitral first sound may be seen to be delayed in the left heart phonocardiogram occurring 0.0[illegible] sec. after the Q wave. It is not seen on the external tracing, because it is masked by the ejection sound. The ejection sound is generated in the pulmonary artery and therefore is not recordable in the left heart chamber.

*Case 7* is that of a 55 year old woman with moderately severe rheumatic aortic insufficiency, mild to moderate mitral insufficiency and minimal mitral stenosis. The murmur generated during regurgitation into the left atrium was clearly pansystolic. While the sound pressure recording apparatus was being used in the left ventricular inflow tract, a whoop was generated in late systole (Fig. 7). The whoop is typical of many naturally occurring whoops in that it occupied the latter part of systole, extended up to the sound of aortic valve closure and varied in intensity from beat to beat. Minor variations in the position of the catheter caused this phenomenon to disappear or reappear, presumably because of varying tension on the mitral valve. The whoop was much greater in intensity externally than in the left ventricular cavity. This fact plus the late systolic timing and variation of the whoop with minor changes in the position of the catheter indicate that the whoop was generated at the mitral valve and that it radiated in the direction of the mitral regurgitant pathway into the left atrium rather than into the ventricle.

The late systolic timing and high frequency recording characteristics of the late systolic whoop are similar to those seen in the intracardiac murmur in Case 4 (see Fig. 4). This similarity and the regurgitant radiation of the whoop raise the possibility that naturally occurring late systolic whoops might be representative of minimal late mitral insufficiency, perhaps due to

abnormal attachment of chordae tendineae or dysfunction of a papillary muscle related or not to myocardial infarction.[13] Several patients with systolic whoops have had arteriosclerotic heart disease[4] and 1 patient known to the authors but not reported in this study had laboratory and autopsy evidence of mitral insufficiency, previous myocardial infarction and an abnormal papillary muscle.

*Case 8* is that of a 55 year-old man with a 7 year history of progressive cardiomegaly of obscure etiology. There were no signs or symptoms of coronary artery occlusive disease but severe congestive failure had been present for 1 year prior to investigation. A moderately high pitched systolic whoop was audible at the bedside. The whoop was present on full inspiration and usually absent on expiration. It was also prominent in the first few beats after an extrasystole. Its duration, timing and intensity varied from time to time although it was never heard in diastole or during the period of ventricular isovolumetric contraction. A Grade 1 pansystolic murmur of mitral insufficiency was also audible. The systolic whoop recorded above the mitral orifice (Fig. 8) was of greater intensity than when recorded below the mitral valve or elsewhere within the left heart or externally. It was not heard in the right heart. The whoop had its onset after isovolumetric systole and was of variable duration. The pansystolic regurgitant murmur had the same distribution as the whoop. During the recording of Fig. 8 there were no catheters traversing the mitral valve, thus excluding the phenomenon noted in the previous case.

Because of its respiratory and positional variation this whoop previously would have been considered to arise from an extracardiac mechanism. However, the regurgitant nature of this whoop is clearly revealed by the left heart sound pressure recordings. Cineangiocardiograms documented the presence of slight mitral in-

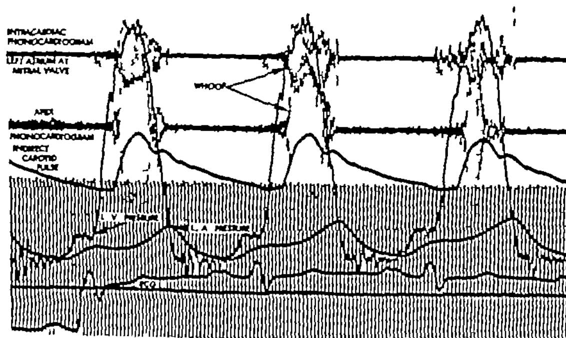



Fig. 8. A 55 year-old man with primary myocardial disease and mitral insufficiency and an intermittent systolic whoop recorded best above the mitral valve. The whoop has the intracardiac distribution and radiation of a mitral regurgitant murmur. Its presence varies with respiration, body position and the presence of ventricular extrasystoles. Its intensity and duration varies from beat to beat. The murmur extends through and masks the sounds of valve closure. Left ventricular pressure was obtained through a retrograde aortic catheter.

Fig. 9. A 57 year-old woman with sinus rhythm and left bundle branch block (ECG). The whoop occurring during isovolumetric contraction [illegible] identified in the apical phonocardiogram (upper [illegible] right). With intracardiac recording, the whoop [illegible] localized to the left ventricular inflow tract. It begins with the first sound [illegible] the onset [illegible] ventricular contraction [illegible] and terminates prior to the onset of ejection (left lower [illegible]) thus limiting the whoop to the isovolumetric contraction period.

competence and what appeared to be adequate coronary vessel.

*Case 9* is that of a 57 year-old woman who was hospitalized because of acute bronchitis. There was no previous history of rheumatic fever or pericarditis and the patient had no cardiovascular symptoms. Left bundle branch block was found on a routine electrocardiogram. An early systolic whoop beginning with the first sound was recorded externally and with the intracardiac microphone; this whoop was localized to the left ventricular inflow tract in the region of the mitral chordae (Fig. 9). This whoop occurred during the period of isovolumetric contraction. At this time the papillary muscles are putting the chordae tendineae on the stretch to fix the mitral valve in the closed position. All left heart pressures were normal and there was no evidence of mitral insufficiency or stenosis.

## Discussion

The evaluation and interpretation of murmurs and other acoustical events recorded within the left atrium should not be approached casually. It is important to realize that in some instances the same mitral regurgitant murmur has different durations and configurations when recorded in various areas of the atrium.[9] This is best explained by the cineangiographic demonstration of the mitral regurgitant jet being played across the atrium in much the same fashion as one applies paint with a paint spray. Thus it is possible in any particular part of the atrium to sample only a portion of a murmur. It is obvious then that the only area

in which mitral regurgitant acoustical events may be recorded with certainty in the area of the mitral orifice. A good technique for assuring adequate sampling of the mitral orifice is to withdraw the recording device from the body of the left ventricle into the left atrium during recording.

As a result of study of these 9 patients with transseptal sound and pressure methods simultaneously, the late systolic murmur has been shown to be a mitral regurgitant murmur in the 5 cases in which it was present. In addition, the mitral origin of three systolic clicks has been clearly demonstrated, one introducing late systolic mitral regurgitation, another probably related to a bulging posterior leaflet, and a third terminating an early systolic regurgitant murmur. Two instances of systolic whoop have been shown to be mitral regurgitant phenomena, and an early systolic whoop occurring during isovolumetric contraction has been localized to the region of the chordae tendineae. One of the regurgitant whoops was limited to late systole, whereas the other varied in duration. The precise localizing nature of the technique employed has proved that all of these acoustical events arise directly from the mitral valve and its supporting structures.

It has long been appreciated that the usual case of mitral insufficiency, regardless of etiology, may be recognized by the presence of a typical pansystolic regurgitant murmur. For many years late systolic murmurs, systolic clicks, and whoops were thought to arise from extracardiac mechanisms and, for the most part, not to reflect significant mitral pathology. The evidence supporting these impressions was mostly circumstantial. It has certainly been thought by most observers that a large number of patients with these physical findings had histories of pleural and pericardial disease, but the pericardial disease was often rheumatic.[1]

Recently it has been shown that some late systolic murmurs, whether introduced by a click or not, are associated with mild mitral regurgitation. In addition, it is now apparent that systolic whoops reflect mitral insufficiency in some cases and that late systolic murmurs, clicks, and whoops make up the auscultatory continuum of mild mitral insufficiency.

The high incidence of pericardial disease in patients with late systolic murmurs and systolic clicks should not be dismissed lightly. Perhaps in some cases pericardial inflammation and thickening might distort the supporting structures of the mitral valve or its annulus or alter the contraction characteristics of papillary muscle, as is suggested by the fact that in Case 1 there was certain evidence of late systolic mitral insufficiency in a patient with a history of pleural and pulmonary metastases and documented pericardial thickening at the time of cardiac investigation.

Even so, it would not be reasonable to infer that every instance of systolic click and whoop represents mitral insufficiency. These events can and do arise from other cardiac valves and perhaps by other mechanisms.

## Summary

Nine patients were studied by means of a modification of the Ross transseptal catheterization technique which permits simultaneous recording of sound and pressure in the left heart chambers. In the 5 patients with late systolic murmurs, these murmurs were shown to arise in the mitral area and to radiate into the left atrium, thus documenting their regurgitant nature. One of these patients had a thickened pericardium. Three instances of systolic clicks were localized to the mitral valve, one with late mitral insufficiency probably due to a prolapsed leaflet, one introducing a late regurgitant murmur, and the third terminating an early regurgitant murmur. A late systolic whoop, artifically induced, was found to be regurgitant in character, and a late systolic whoop of varying duration, naturally occurring, was also found to be regurgitant. An early systolic whoop occurring during isovolumetric contraction was localized to the subvalvular supporting structure. It has become apparent from the study of these cases that late systolic murmurs, systolic clicks, and systolic whoops constitute a continuum of acoustical events which are associated with mitral insufficiency.

Some speculation has been made concerning the possible relationship of pericardial disease and these mitral acoustical events.

## Addendum

Since the preparation of this manuscript a case of late systolic murmur introduced by a click has been shown by Perloff Ronan and Harvey[14] to emanate from the mitral valve

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# Experimental and laboratory reports

## The pulmonary hemodynamic effects of amyl nitrite in normal man

*Antonio C. de Leon, Jr., M.D.*
*Joseph K. Perloff, M.D.*
*Washington, D. C.*

Vasoactive drugs have assumed roles of increasing importance in cardiac auscultation and in the phonocardiographic and hemodynamic assessment of heart disease. Amyl nitrite, a drug in this category, has proved to be a safe, simple, and reliable diagnostic adjunct.[1-4] Inferences drawn from the circulatory effects of amyl nitrite in disease states benefit from a clearer appreciation of its effects in normal subjects. Although the drug has been used for nearly a century,[7] knowledge of its action on the normal circulation remains incomplete. Accordingly, the systemic hemodynamic effects of the inhalation of amyl nitrite in normal man were recently studied in this laboratory,[8] and the present investigation was undertaken in order to extend these observations to the pulmonary circulation.

#### Materials and methods

Observations were made on 18 healthy volunteers under light pentobarbital sedation (100 mg.). All were carefully screened in order to exclude clinically evident cardiovascular disease. There were 17 males and 1 female. They ranged in age from 20 to 30 years (mean of 25 years). The nature of each procedure was explained in detail in order to minimize apprehension. Because of the possibility that the circulatory effects of amyl nitrite might differ in older subjects, those above 40 years of age were excluded. All observations were made with the patients supine. A Cournand catheter was introduced into the pulmonary artery (via a median basilic vein) using standard methods of right heart catheterization. Indwelling Cournand needles were inserted into both right and left brachial arteries. The methods of instrumentation, calibration, and data analysis were similar to those previously described.

Amyl nitrite was inhaled from a broken phial while the subject breathed quietly for 10 to 20 seconds until the brachial arterial systolic pressure fell 30 to 40 mm. Hg.

*Part I.* Control observations, generally in duplicate, were made while simultaneously recording the electrocardiogram, the mean pulmonary arterial and brachial arterial pressures, and an indicator-dilution curve for cardiac output. Calibrated amounts of indocyanine green dye were injected into the pulmonary artery (transiently interrupting the mean pressure tracing), and dilution curves were inscribed by withdrawal from a brachial artery. Similar

From the Department of Medicine, Georgetown University School of Medicine, Division of Cardiology, Georgetown University Hospital, Washington, D. C.
Supported in part by United States Public Health Service Grant HE-[illegible] and by Public Health Service Career Program Award HE [illegible]. A portion of this work was conducted through the Georgetown University Clinical Study Unit, supported by the [illegible] (FR-[illegible]).
Received for publication [illegible] 21, [illegible].
[illegible] Georgetown University Hospital, 3800 Reservoir Rd., N.W., Washington, D. C. [illegible]

*Table* I *Part I*

| *Parameter* | *Cardiac index (L/min/M²)* | *Stroke volume index (cc/M²)* | *Mean pulm art pressure (mm Hg)* | *Mean brachial art pressure (mm Hg)* | *RV minute work index (Kg M/M²)* |
|---|---|---|---|---|---|
| Control | 3.75 (2.7–4.9) | 49.5 (34–56) | 12.8 (8.5–18) | 91.0 (80–111) | 0.66 (0.44–0.99) |
| Test | 6.24 (4.4–7.8) | 54.3 (43–72) | 15.1 (11–19) | 59.0 (43–80) | 1.30 (0.74–1.86) |
| Per cent change | +66 | +10 | +18 | −35 | +95 |
| p Value | <0.001 | <0.02 | <0.001 | <0.001 | <0.001 |

*Table* II *Part II*

| *Parameter* | *Pulmonary arterial systolic pressure (mm Hg)* | *Pulmonary arterial diastolic pressure (mm Hg)* | *RV systolic pressure (mm Hg)* | *RV diastolic pressure (mm Hg)* | *Brachial arterial systolic pressure (mm Hg)* | *Brachial arterial diastolic pressure (mm Hg)* |
|---|---|---|---|---|---|---|
| Control | 19 (13–26) | 8.2 (4–17) | 25 (15–35) | 4.3 (2–9) | 116 (100–148) | 72 (54–90) |
| Test | 23 (17–32) | 8.7 (4–19) | 27 (19–37) | 2.7 (1–4) | 84 (58–104) | 47 (36–58) |
| Per cent change | +22 | +7 | +8 | −38 | −27.6 | −34.5 |
| p Value | < 0.001 | 0.5 | < 0.01 | < 0.05 | 0.001 | 0.001 |

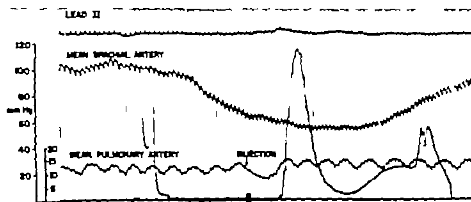



Fig. 1 Simultaneously recorded mean brachial and pulmonary arterial pressures with a quantitative indicator dilution curve inscribed after inhalation of amyl nitrite. There is a rise in the mean pulmonary arterial tracing at the time of maximal decline in systemic arterial pressure. See text for details.

| RV stroke work index (Gm M/M²) | LV minute work index (Kg M/M²) | LV stroke work index (Gm M/M²) | Pulmonary vascular resistance (dynes sec cm⁻⁵) | Systemic vascular resistance (dynes sec cm⁻⁵) | Heart rate (per min) | Recirculation time (sec) |
|---|---|---|---|---|---|---|
| 8 8 (5 6–13 7) | 4 40 (2 8–6 0) | 56 2 (25 6–87) | 146 (85–309) | 944 (654–1478) | 77 (60–90) | 11 7 (14–18) |
| 11 7 (8 0–16 4) | 4 68 (2 76–6 65) | 40 8 (31–58 5) | 95 (60–176) | 414 (270–822) | 115 (96–138) | 8 4 (7–10) |
| +27 | +7 | −27 | −33 | −56 | +50 | −28 |
| <0 01 | 0 5 | <0 01 | <0 01 | <0 001 | <0 001 | <0 001 |




Fig 2 At the onset of the decline in brachial arterial pressure there is a rise in mean pulmonary arterial pressure which is maintained for the duration of the decline in systemic pressure See text for details

observations were then made after the inhalation of amyl nitrite (Figs 1 and 2) The following data were derived (Table I) cardiac index stroke index mean pulmonary arterial and brachial arterial pressures right ventricular and left ventricular minute and stroke work indices total pulmonary and systemic vascular resistances heart rate and mean recirculation time of injected indicator

*Part II* Thirty minutes after the initial inhalation of amyl nitrite sequential control tracings were taken of the undamped pulmonary arterial and right ventricular pressures while simultaneously recording the undamped brachial arterial pressure and the electrocardiogram The catheter was readvanced into the pulmonary artery and similar observations were made at the height of the amyl nitrite effect The systolic and diastolic pressures in the pulmonary artery right ventricle and brachial artery were then measured (Table II)

*Part III* Twenty to 30 minutes after completion of Part II the following observations were made on 3 subjects Calibrated amounts of indocyanine green dye were injected into a large median basilic vein via a No PE 50 polyethylene catheter and dilution curves were inscribed by withdrawal from the pulmonary artery via the intracardiac catheter Similar tracings were recorded at the height of the amyl nitrite effect (Fig 3) It is recognized that the use of a cardiac catheter as the afferent limb of the withdrawal system may introduce inaccuracies in the absolute values of flow determina

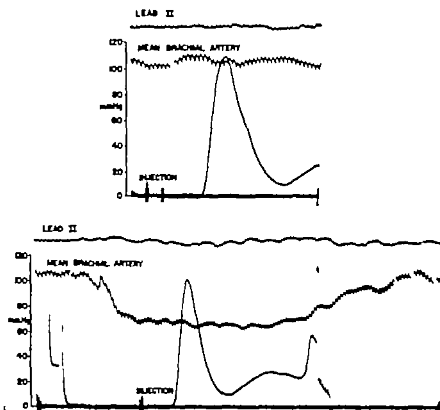



Fig. 3. *Upper.* Mean brachial arterial pressure and a control dilution curve obtained by withdrawal from the pulmonary artery via the catheter after injection of Cardiogreen into a median basilic vein. *Lower.* The same tracings after the inhalation of amyl nitrite. The area under the dilution curve has diminished, reflecting an increase in flow.

tions.[9] However, the method was not employed for the calculation of absolute values. The dilution curves were used only for *comparative* quantification in order to estimate *directional* changes in pulmonary blood flow, with each patient serving as his own control.

## Results

*Part I (Table I)*

CARDIAC OUTPUT. The average control cardiac index was 3.75 L./min./M.² with a range of 2.7 to 4.9. At the height of the amyl nitrite effect the average was 6.24 L./min./M.² with a range of 4.47 to 7.8, representing a significant increase of 66 per cent ($p < 0.001$).

STROKE VOLUME. The average control stroke volume index was 49.5 ml./M.² with a range of 34 to 56. At the height of the amyl nitrite effect the average was 54.3 ml./M.², with a range of 43 to 72, representing a slight increase of 10 per cent ($p < 0.02$).

MEAN PULMONARY ARTERIAL PRESSURE. The average control mean pulmonary arterial pressure was 12.8 mm. Hg with a range of 8.5 to 18. At the height of the amyl nitrite effect the average was 15.1 mm. Hg with a range of 11 to 19, representing a small but significant increase of 18 per cent ($p < 0.001$).

In 4 instances there was a rise of 2 to 4 mm. Hg in mean pulmonary arterial pressure at the onset of the fall in brachial arterial pressure.

MEAN BRACHIAL ARTERIAL PRESSURE. The average control brachial arterial mean pressure was 91 mm. Hg with a range of 60 to 111. At the height of the amyl nitrite effect the average was 59 mm. Hg with a range of 43 to 80, representing a significant decline of 35 per cent ($p < 0.001$).

RIGHT VENTRICULAR MINUTE WORK. The

average control effective right ventricular minute work index was 0.66 Kg.M./M.² with a range of 0.44 to 0.99. At the height of the amyl nitrite effect the average was 1.30 Kg.M./M.² with a range of 0.74 to 1.66, representing a significant increase of 95 per cent ($p < 0.001$).

LEFT VENTRICULAR MINUTE WORK. The average control effective left ventricular minute work index was 4.40 Kg.M./M.² with a range of 2.8 to 6.0. At the height of the amyl nitrite effect the average was 4.68 Kg.M./M.² with a range of 2.76 to 6.65, representing an insignificant change of 7 per cent ($p < 0.5$).

RIGHT VENTRICULAR STROKE WORK. The average control effective right ventricular stroke index was 8.8 Gm.M./M.² with a range of 5.6 to 13.7. At the height of the amyl nitrite effect the average was 11.2 Gm.M./M.² with a range of 8.0 to 16.4, representing a significant increase of 27 per cent ($p < 0.01$).

LEFT VENTRICULAR STROKE WORK. The average control effective left ventricular stroke work index was 56.2 Gm.M./M.² with a range of 25.6 to 82. At the height of the amyl nitrite effect the average was 40.8 Gm.M./M.² with a range of 31 to 58.5, representing a significant decline of 27 per cent ($p < 0.01$).

PULMONARY VASCULAR RESISTANCE. The average control total pulmonary vascular resistance was 146 dynes sec. cm.⁻⁵ with a range of 85 to 309. At the height of the amyl nitrite effect the average was 98 dynes sec. cm.⁻⁵ with a range of 60 to 176, representing a significant decline of 33 per cent ($p < 0.01$).

SYSTEMIC VASCULAR RESISTANCE. The average control systemic vascular resistance was 944 dynes sec. cm.⁻⁵ with a range of 654 to 1,458. At the height of the amyl nitrite effect the average was 414 dynes sec. cm.⁻⁵ with a range of 270 to 522, representing a significant decline of 56 per cent ($p < 0.001$).

HEART RATE. The average control heart rate was 77 beats per minute with a range of 60 to 90. At the height of the amyl nitrite effect the average was 115 per minute with a range of 96 to 138, representing a significant increase of 50 per cent ($p < 0.001$).

CIRCULATION TIME. The average control recirculation time was 11.7 seconds with a range of 14 to 18. At the height of the amyl nitrite effect the average was 8.4 seconds with a range of 7 to 10, representing a significant decline of 28 per cent ($p < 0.001$).

*Part II (Table II)*

PULMONARY ARTERIAL SYSTOLIC PRESSURE. The average control pulmonary arterial systolic pressure was 19 mm. Hg with a range of 13 to 26. At the height of the amyl nitrite effect the average was 23 mm. Hg with a range of 17 to 32, representing a significant increase of 22 per cent ($p < 0.001$).

PULMONARY ARTERIAL DIASTOLIC PRESSURE. The average control pulmonary arterial diastolic pressure was 8.2 mm. Hg with a range of 4 to 17. At the height of the amyl nitrite effect the average was 8.7 mm. Hg with a range of 4 to 19, representing an insignificant increase of 7 per cent ($p < 0.5$).

RIGHT VENTRICULAR SYSTOLIC PRESSURE. The average control right ventricular systolic pressure was 25 mm. Hg with a range of 15 to 35. At the height of the amyl nitrite effect the average was 27 mm. Hg with a range of 19 to 37, representing a small but significant increase of 8 per cent ($p < 0.01$).

RIGHT VENTRICULAR DIASTOLIC PRESSURE. The average control right ventricular diastolic pressure was 4.3 mm. Hg with a range of 2 to 9. At the height of the amyl nitrite effect the average was 2.7 mm. Hg with a range of 1 to 4, representing a decline of 38 per cent ($p < 0.05$).

BRACHIAL ARTERIAL SYSTOLIC PRESSURE. The average control brachial arterial systolic pressure was 116 mm. Hg with a range of 100 to 148. At the height of the amyl nitrite effect the average was 84 mm. Hg with a range of 58 to 104, representing a significant decline of 27.6 per cent ($p < 0.001$).

BRACHIAL ARTERIAL DIASTOLIC PRESSURE. The average control brachial arterial diastolic pressure was 72 mm. Hg with a range of 54 to 90. At the height of the amyl nitrite effect the average was 47 mm. Hg with a range of 36 to 58, representing a significant decline of 34 per cent ($p < 0.001$).

*Part III*

QUANTIFICATION OF INDICATOR DILUTION CURVES OBTAINED BY PERIPHERAL VENOUS INJECTION WITH PULMONARY ARTERIAL WITHDRAWAL (Fig. 3). The average control quantification was 2.97 L./min./M.² At the height of the amyl nitrite effect the average was 5.38 L./min./M.²

**Discussion**

Amyl nitrite, by interfering with the enzymatic decomposition of adenosine triphosphate, deprives arterial smooth muscle of the energy required for the maintenance of tone, thus initiating vasodilatation.[14] The systemic hemodynamic effects of this pharmacologic intervention include[8]: (1) a decrease in arterial pressure, vascular resistance, stroke work, circulation time, level of the dicrotic notch, amplitude of the dicrotic wave, and duration of the diastolic filling period; (2) an increase in heart rate, cardiac index, and ejection velocity; and (3) no change in stroke volume or minute work. During the course of the present study, many of these systemic circulatory parameters were of necessity reinvestigated and the findings were in close agreement with prior observations.[8]

*Effects on pressure and flow in the pulmonary circulation.* Amyl nitrite causes a marked, consistent increase in systemic flow per minute.[2,8] Whether the drug exerts a similar effect on pulmonary blood flow has been unsettled. In the dog, nitroglycerin increases left ventricular output more than it increases venous return to the right heart, the difference being derived from the thoracic reservoir.[11] However, this reservoir appears to be insufficient to permit increases in systemic output of the degree induced by amyl nitrite unless a commensurate increase in venous return occurs.[8] This thesis is supported by the uniform rise in right ventricular systolic pressure after the inhalation of amyl nitrite by patients with pulmonary stenosis[8] and is in accord with the small but significant increases in both systolic and mean pulmonary arterial pressures after the administration of amyl nitrite in this study (Fig. 2, Tables I and II). Estimates of nitrite-induced directional changes in pulmonary blood flow in 3 subjects so studied (Fig. 3) suggested that venous return increased roughly in parallel with the augmentation of systemic output. Should an increase in venous return be of the same order as the increment in cardiac output, then the pulmonary vascular resistance would of necessity decline (Table I). However, the magnitude of this decline is far less than the fall in systemic resistance (Table I).[6,8] These data do not indicate whether the lesser circulation dilates passively to accommodate the increase in flow or whether amyl nitrite exerts a direct vasodilatory effect. The drug does appear to act as an active dilator in the vasoconstrictive pulmonary hypertension of large ventricular septal defect in which the left-to-right shunt provides a pathway for the entry of relatively undiluted nitrite into the pulmonary circulation.[11] Response to the drug in this context may therefore relate to the increased concentration of active principle acting upon highly vasoreactive arterioles.[11] In the presence of a normal circulation, relatively dilute nitrite enters a less reactive pulmonary bed. Although the drug may still exert a direct effect in normal man, additional passive dilatation remains a plausible consideration with regard to the primary pharmacologic influence on the pulmonary vascular resistance.[4]

The small but significant nitrite-induced rise in pulmonary systolic pressure with *little or no change in diastolic pressure* resulted in a modest increase in pulse pressure (Table II). The contour of the pulmonary arterial pulse, including the level of the dicrotic notch, remained unchanged after the inhalation of amyl nitrite in contrast to the marked alterations in systemic arterial contour.[8] There was a slight but significant increase in right ventricular systolic pressure with a 38 per cent decline in diastolic filling pressure (borderline significance) (Table II).

Opinion differs with regard to the effect of amyl nitrite upon the systemic *venous* bed; some authors hold that the drug induces venoconstriction,[13] whereas others believe that venodilatation occurs.[14] In dogs on right heart bypass with fixed systemic outputs,[14] amyl nitrite induces an initial transient *increase* in venous return as the systemic arterial pressure begins

to fall but subsequently induces a *decrease* in venous return as the systemic pressure falls maximally. These observations suggest that the initial effect is reflex venoconstriction in response to the fall in systemic arterial pressure and that the subsequent effect is venodilatation in response to the direct effect of the drug upon the venous bed. In the light of this information it was pertinent that 4 of our subjects showed a small distinct rise in mean pulmonary arterial pressure at the onset of the fall in brachial arterial pressure (Fig. 2). This suggests that in man the inhalation of amyl nitrite may induce an initial increase in venous return due to transient venoconstriction followed by an additional increase in venous return associated with augmented cardiac output.

*Effect on ventricular work (Table I).* Since amyl nitrite caused only a moderate decline in pulmonary resistance the mean pulmonary arterial pressure rose slightly in the face of the large increment in flow. Accordingly right ventricular minute work increased appreciably. Furthermore the rise in pulmonary mean pressure occurred with a relatively constant stroke volume so that right ventricular stroke work rose although to a lesser degree than work per minute.

These results were in marked contrast to the effect of amyl nitrite on *left* ventricular work.[3] The increase in cardiac output was uniformly associated with a fall in systemic arterial pressure that was sufficient to leave left ventricular minute work relatively constant. Since stroke volume changed little if at all as systemic pressure fell, left ventricular stroke work regularly and strikingly decreased. Thus amyl nitrite had opposite effects upon the two ventricles and appeared to be a pharmacologic means of selectively stressing the right heart.

*Diagnostic implications of the foregoing effects of amyl nitrite.* Under the influence of amyl nitrite the gradient and murmur of tricuspid stenosis increase because of augmented flow into the right atrium together with a shortened diastolic filling period.[14] As the right ventricle is stressed, tricuspid regurgitant flow should increase and the murmur of tricuspid incompetence should get louder.[4] In pulmonary stenosis with intact ventricular septum[2] the increase in circulatory flow rate and venous return augment both the gradient and the murmur. In patients with mild pulmonary stenosis and nondiagnostic gradients, the inhalation of amyl nitrite may induce a significant difference in right ventricular–pulmonary arterial systolic pressures in a fashion analogous to the effect of the drug in occult obstruction to left ventricular outflow.[4] In cyanosed Fallot's tetralogy[2] the ventricular septal defect permits the right ventricular pressure to fall in parallel with the decline in systemic pressure so that the right-to-left shunt increases, the pulmonary flow diminishes, and the murmur becomes shorter and softer. Maintenance of pulmonary arterial diastolic pressure in nonvasoreactive pulmonary hypertension should prevent a decrease in the Graham Steell murmur whereas a uniform fall in systemic diastolic pressure regularly reduces the intensity of the murmur of aortic incompetence. The disproportionate fall in systemic vascular resistance diminishes left-to-right shunts through nonpulmonary hypertensive aortopulmonary or interventricular communications. On the other hand in the presence of patent ductus with fixed pulmonary hypertension and a balanced shunt, the inhalation of amyl nitrite may cause diagnostic differential cyanosis by selectively decreasing systemic arterial pressure.


## Summary

Amyl nitrite has assumed a role of considerable importance in clinical auscultation of the heart and in the phonocardiographic and physiologic evaluation of the cardiac patient. The systemic hemodynamic effects of the inhalation of amyl nitrite were recently investigated in this laboratory. The purpose of the present study was to extend these observations to the lesser circulation.

Results indicate that the inhalation of amyl nitrite in normal man causes (1) a marked increase in blood flow which is primarily rate related, (2) a profound decline in total systemic resistance resulting in a decline in left ventricular stroke work but no change in left ventricular minute work, (3) a less profound decline in total

pulmonary resistance; (4) a small but significant rise in pulmonary arterial systolic and mean pressures; and (5) an increase in effective right ventricular minute and stroke work. Diagnostic implications were briefly discussed. Knowledge of the circulatory action of the drug in normal man should enhance its usefulness in disease states.

The author ... thank Dr. ... A. R. ... Dr. Peter A. Bran... ... each of whom participated in ... of the studies. We also wish to acknowledge the ... assistance of Rosemary C. ... Chief Nurse, Cardiac Diagnostic Laboratory.

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# Optical behavior of indocyanine green dye in blood and in aqueous solution


*William F. Sutterer, B.S.**
*Schuyler E. Hardin*
*Robert W. Benson*
*L. Jerome Krovetz, M.D., Ph.D.*
*Gerald L. Schiebler, M.D.*
*Gainesville, Fla.*


One major advantage of the use of indocyanine green† dye for indicator dilution curves is the occurrence of its maximum light absorption at a wave length of 800 millimicrons in plasma. This dye thus facilitates recording of indicator dilution curves independent of variations in oxygen saturation.[1,2]

The use of the dye dilution technique for the determination of cardiac output and/or the magnitude of shunts necessitates calibration of the sensitivity of the densitometer to known concentrations of blood-dye mixtures. It follows that the densitometer must be stable and capable of giving an identical output for any given concentration of dye in whole blood. Techniques and instruments have been developed which are capable of recording calibration curves to this high degree of accuracy. These techniques and instrumentation have been used successfully for a number of years. Recently, however, at the University of Florida Teaching Hospital there was a period of time during which it was virtually impossible to obtain stable and reproducible dye dilution calibration curves with the use of Cardio-Green dye in heparinized fresh whole blood. Extensive checks of the densitometers determined that they were operating satisfactorily. It was found that fresh blood heparinized with an anticoagulant known as Lipo-Hepin‡ which contains a small amount of sodium bisulfite used as a preservative caused a significant and apparently erratic decrease in light absorption and vitiated the calibration. Correspondence with other laboratories showed that they had had similar experiences.

Therefore, the purpose of this paper is to draw attention to the behavior of indocyanine green dye in the presence of sodium bisulfite and in aqueous solutions. Empirical data and a discussion are offered for consideration by those using these dye dilution techniques. Although the optical


From the Department of Pediatrics [illegible] Cardiovascular Laboratory [illegible] Health [illegible] of Florida, Gainesville, Fla.
Supported [illegible] Training Grant [illegible] Development [illegible] Grant No. [illegible] Health [illegible] Florida Heart Association [illegible] Grant No. [illegible]
Received for publication Dec. [illegible]


*Address: Department of Pediatrics, University of Florida School of Medicine, Gainesville, Fla. [illegible]
†Distributed under the brand name of Cardio-Green dye by Hynson, Westcott & Dunning, Inc., Baltimore [illegible]
‡Riker Laboratories, Inc., Northridge, Calif.

behavior of indocyanine green dye discussed in this communication is well known to dye chemists, it has been often overlooked by people using this dye for diagnostic and investigative procedures.

*Effect of Lipo-Hepin and Liquaemin Sodium "10" on static calibration of the densitometer.* Blood was withdrawn from normal subjects and half of it was heparinized with Liquaemin Sodium "10"[*] and half with Lipo-Hepin. Both of these anticoagulants are rendered isotonic by the addition of sodium chloride, and sodium hydroxide is added to adjust the pH of Lipo-Hepin to a mean value of 7 with a range of 6.8 to 7.2,[6] whereas the pH of Liquaemin Sodium "10" is adjusted to a mean value of approximately 6.8 with a range of 6.5 to 7.5.[7] Two sets of dye dilutions were made, each set consisting of three concentrations of dye at 0, 6, and 12 mg. per liter. These samples were then drawn through a densitometer† by a constant withdrawal syringe set at 1.91 c.c. per minute‡ and the output of the densitometer was recorded on an 1108 Honeywell Visicorder. The resulting calibration curves are shown in Fig. 1. Notice the marked difference in the recorded deflections of the galvanometer for identical concentrations of dye.

Loss of light absorption of approximately equal magnitude was demonstrated repeatedly with the use of fresh whole blood anticoagulated with Lipo-Hepin. Moreover, a similar phenomenon has been observed approximately thirty times in diagnostic procedures when Lipo-Hepin was used. Absorption of light at 800 mμ was also found to be extremely unstable with respect to time. Dye-blood solutions anticoagulated with Lipo-Hepin often changed with time from that shown in Fig. 1 to a calibration curve similar to that seen when the blood was heparinized with Liquaemin Sodium "10."

*Effect of Lipo-Hepin and Liquaemin Sodium "10" on absorption of indocyanine green dye in citrated whole blood.* Five out of six observations with Lipo-Hepin used as the anticoagulant for fresh whole blood

*Organon Inc., West Orange, N. J.
†Waters XC 100A densitometer manufactured by Waters Corp., Rochester, Minn.
‡Harvard syringe set at speed 3 with the use of 50-c.c. syringe.

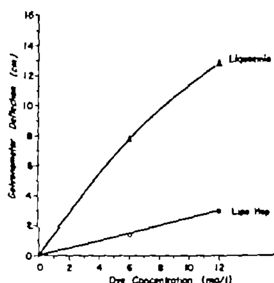



Fig. 1. Effect of Lipo-Hepin and Liquaemin sodium "10" on the absorption of 800 mμ of light by indocyanine green dye in fresh whole blood. The optical densities of the blank blood as measured by the Waters XC 100A densitometer are 0.70 and 0.72 for Liquaemin and Lipo-Hepin, respectively. This indicates that the presence of these heparin solutions does not cause a nonspecific effect in the blank blood of a magnitude great enough to affect the calibration of the background-dye compensated XC 100A.[8,11] However, it does not rule out the possibility that a nonspecific effect may be present when Lipo-Hepin, blood, and indocyanine green are mixed.

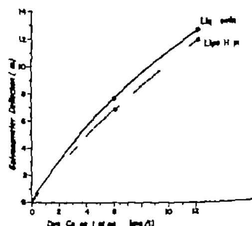


Fig. 2. Effect of Lipo-Hepin and Liquaemin sodium "10" on indicator-dilution calibration curves of indocyanine green dye in citrated blood. Little decrease in the absorption of light at 800 mμ is seen in the set of dye dilutions containing 0.2 c.c. of Lipo-Hepin per 5 c.c. of blood-dye solutions.

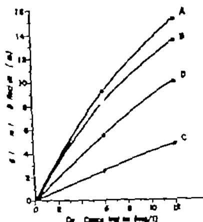



Fig 3 Effect of various colorless solutions on absorption of indocyanine green dye in fresh whole blood All sets of dye dilution contain laboratory prepared sodium heparin mixed with isotonic saline to a concentration of 1 000 units of heparin per cubic centimeter of solution The optical densities of the samples of blank blood as measured by the NC 100A densitometer (peak sensitivity at a wave length of approximately 800 mμ) are Set $A$ = 0 77 $B$ = 0 73 $C$ = 0 75 and $D$ = 0 75

with no other additive present showed a decrease in light absorption At no time was this marked decrease in absorption observed in any studies in which dye and Lipo-Hepin or Liquaemin Sodium 10 were added to citrated blood (Fig 2)

*Effect of various colorless solutions on absorption of indocyanine green dye in fresh whole blood* Lipo-Hepin unlike Liquaemin Sodium 10 contains 0 1 per cent sodium bisulfite in addition to the benzyl alcohol used as a preservative in both Therefore benzyl alcohol and sodium bisulfite solutions were added separately to fresh blood dye mixtures of known concentrations and drawn through the densitometer in the standard method for calibrating the instrument The anticoagulant used was laboratory prepared heparin* at a concentration of 40 units per cubic centimeter of blood

The effect of these solutions on identical concentrations of dye blood solutions of 0 6 and 12 mg per liter of dye concentrations is shown in Fig 3 Curve $A$ is the calibration obtained from the set of dye dilutions to which 0 2 c c of distilled water per 5 c c of blood dye solution was added to keep the dilution the same for all solutions This curve exhibited the greatest absorption of light as sensed by the densitometer Slightly less absorption of light at a wave length of 800 mμ was seen when 0 2 c c of 0 9 per cent benzyl alcohol was added to each 5 c c of blood dye solution (curve $B$)

The addition of 0 2 c c of 0 1 per cent sodium bisulfite to 5 c c of blood dye dilution (curve $C$) resulted in a marked decrease in absorption When 0 2 c c of 0 9 per cent benzyl alcohol and 0 1 per cent sodium bisulfite were added to 5 c c of solution a light absorption intermediate between $B$ and $C$ was found (curve $D$)

The spectral absorption of these additives as well as of Lipo-Hepin and Liquaemin Sodium 10 were studied from a wave length of 650 mμ to 1 μ and found to be very nearly the same as that of water At wave lengths between 900 mμ and 1μ benzyl alcohol transmits more light than water

*Effect of colorless solutions on absorption of indocyanine green dye* Speculation arose as to whether this reduction in light absorption at 800 mμ was due to a change in the structure of the dye molecule because of the presence of sodium bisulfite thus changing the wave length of peak absorption Dye and distilled water solutions were made and combined with various colorless solutions used as additives A water dye solution with the same dye concentration for all solutions was used as the control As shown in Fig 4 a marked decrease in optical density of the dye solutions was observed in the sample containing sodium bisulfite (curve $D$) A significant difference in optical density between the control sample (curve $C$) and the sample containing Lipo Hepin (curve $A$) was not observed with a concentration of 0 2 c c of Lipo-Hepin in 5 c c of dye water solution nor were there any optical suggestions of either polymolecular aggregation or polymerization over the wave lengths studied

*Effect of time on indocyanine green dye in aqueous solution* An aqueous solution of indocyanine green in a concentration of 1 25 mg per cubic centimeter kept in

*Heparin crystal dissolved in isotonic saline to give concentration of 1,000 units per cubic centimeter

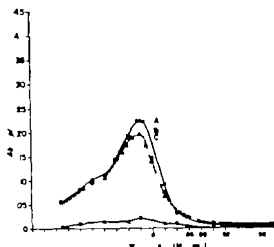


Fig. 4. Spectral absorption curves of dye and water solution with various colorless additives. Solutions are of 5 c.c. distilled water plus 0.006 c.c. of 1.25 mg. per cubic centimeter dye (Hynson, Westcott & Dunning special diluent used to dissolve the dye) and 0.2 c.c. of additive. A is the spectral absorption curve for sample with 0.2 c.c. of Lipo-Hepin added. Curves B and C represent absorption curves for sample containing 0.2 c.c. of Liquaemin Sodium 10 and 0.2 c.c. of water (control), respectively, whereas D is the absorption curve observed for aqueous dye dilution containing 0.2 c.c. of sodium bisulfite. Note that no appreciable effect is seen when Lipo-Hepin is added to the dye-water solution as compared to that seen when water and Liquaemin are used as additive. However, the addition of 0.2 c.c. of sodium bisulfite (0.1 per cent) produces a marked decrease in light absorption at all the wave lengths studied.

disturbed for 7 days was found to have shifted in maximal absorption from 780 to 900 mμ. Therefore, it was decided to study the effects of time systematically.

Fresh solutions of a dye concentration of 1.25 mg. per cubic centimeter were made using the special diluent* furnished with the dye and kept at room temperature for varying lengths of time. Each day a sample of this dye was diluted with distilled water to a concentration of 1.5 mg. per liter and its spectral absorption characteristics were studied between 650 mμ and 1 μ. Peak absorption of this concentrated dye solution remained at 780 mμ for 2 to 6 days, although the absolute light absorption at this wave length decreased with time. The solutions studied developed a second absorption peak at a wave length of 900 mμ sometime during the second through the seventh days in solution (Fig. 5). Within 1 to 3 days after its initial appearance, the second peak markedly increased its absorption, as shown by curve C of Fig. 5.

This shift in peak absorption of the dye in solution was also studied by comparing the effects of time and concentration. A concentrated solution (1.25 mg. per cubic centimeter) was made with the diluent furnished with the dye by Hynson, Westcott & Dunning and studied as previously described. In this case the concentrated sample showed a shift in peak absorption to 900 mμ on the sixth day. Light absorption of concentrated aqueous solutions (1.25 mg. per cubic centimeter) aged as long as 9 months was also studied. In every case the peak absorption was found at 900 mμ instead of at 780 mμ.

Two aliquots were diluted with distilled water to a concentration of 1.5 mg. per

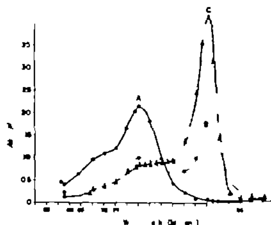


Fig. 5. Effect of time on indocyanine green dye in a concentrated aqueous solution. The dye was kept in solution of a concentration of 1.25 mg. per cubic centimeter and diluted with distilled water to a concentration of 1.5 mg. per liter for spectrophotometric study. Curve A is the observed spectral absorption curve for the dye-water dilution on the same day that it was dissolved in the diluent. Curve B is the absorption curve for the dye in concentrated solution for 6 days, and curve C was observed after the dye was in the 1.25 mg. per cubic centimeter solution for 8 days. This shift in peak absorption to a longer wave length is a well-documented phenomenon for cyanine dyes in aqueous solutions. It is thought to be due to polymolecular aggregation in an orderly array.[38]

*The diluent used is distilled water ... Water for Injection, U.S.P.

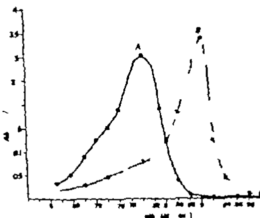



Fig. 6. Spectrophotometric observation of fresh and aged indocyanine green dye in plasma (dye concentration of 1.25 mg. per liter). Curve *A* is spectral absorption curve of fresh dye in plasma and curve *B* is an absorption curve of dye (aged 7 days in concentrated aqueous solution) in plasma.

liter. Oxygen (100 per cent) was bubbled through one of the diluted samples for 10 hours at a rate of 2 L. per minute, and the other sample was left undisturbed. Both solutions were studied hourly for 10 hours and then daily for a total of 7 days. Neither sample exhibited a shift in peak absorption, but after 7 days both had optical densities essentially the same as that of water throughout the wave lengths of 650 mμ to 1 μ.

*Effect of aging* of indocyanine green in plasma.* Spectral absorption of fresh and aged dye plasma solutions was also studied (Fig. 6). Note that the peak absorption of fresh dye in plasma (Fig. 6, curve *A*) was observed at 800 mμ, a shift of 20 mμ from the peak observed in water solution. This observed shift of peak absorption of the fresh dye from 780 mμ (water solution) to 800 mμ in plasma is in close agreement with previous studies by Fox and Wood.[3] However, peak absorption of the aged dye plasma solution was observed at 900 mμ, the same as that seen in the dye water solution (Fig. 6, curve *B*).

## Discussion

Light absorption of indocyanine green dye in fresh whole blood is rendered extremely unstable and is often markedly decreased when Lipo-Hepin is used as an anticoagulant. Because of these observations, the practice of using Lipo-Hepin as an anticoagulant for densitometer calibration of indocyanine green concentration has been discontinued at the University of Florida Teaching Hospital.

Even extremely small quantities of sodium bisulfite decrease light absorption of indocyanine green dye in fresh blood. A marked difference in the optical density of indocyanine green dye in the presence of a procaine solution also containing sodium bisulfite likewise occurs.[4]

When either Lipo-Hepin or sodium bisulfite is added to fresh blood, there is essentially no change in the optical density of the blank blood. This does not rule out the possibility that a nonspecific effect is present when the dye is added to the blood heparinized with Lipo-Hepin. Spectrophotometric studies to date have not shown a shift in spectral absorption of the dye or a decrease in light absorption in the presence of Lipo-Hepin at a concentration of 0.2 c.c. per 5 c.c. of dye solution in either plasma or water over the wave lengths studied (650 mμ to 1 μ) and with the concentrations of Lipo-Hepin used.

Indocyanine green dye in a concentrated aqueous solution (1.25 mg. per cubic centimeter) shifts its peak absorption of light from 780 to 900 mμ between the second and sixth days and then remains the same for at least as long as 9 months. Dilute aqueous solutions (1.5 mg. per liter) did not exhibit this shift in peak absorption but instead decreased light absorption to almost that of water.

Studies of indocyanine green dye in blood plasma have shown this dye to be bound by the plasma proteins, specifically the albumin. The shift in peak absorption of the dye from 780 mμ in water to 800 mμ in plasma is additional evidence that this dye is bound to the blood albumin. Conversely, therefore, the absence of a shift in peak absorption of the aged dye solution in plasma is some evidence that the dye, after polymolecular aggregation occurs, is not bound to plasma proteins. However, electrophoretic and ultracentrifugation studies on the aggregated dye in plasma have not been performed.

*[illegible] concentrated [illegible] for 7 days.

These observations of optical behavior of this dye in concentrated and dilute solutions with respect to time are in agreement with other studies of cyanine dyes in aqueous solution The shift of peak absorption to a longer wave length is probably due to a reversible polymolecular aggregation [8] as discussed previously

## Summary

Indocyanine green dye in the presence of sodium bisulfite exhibits a marked and extremely variable decrease in light absorption Even the presence of the extremely minute quantity present in Lipo Hepin when used as an anticoagulant will vitiate densitometer calibration

Spectrophotometric studies of aqueous solutions of dye in the presence of Lipo Hepin do not show a marked change in light absorption of the dye Stronger solutions of sodium bisulfite produced a marked decrease in light absorption over these wave lengths

Indocyanine green dye kept in a concentrated aqueous solution for periods up to 7 days shifts its peak absorption from 780 to 900 mμ This shift in peak absorption is probably due to reversible polymolecular aggregation

As previously reported fresh solutions of indocyanine green in plasma have an absorption maximum at 800 mμ Peak absorption of aged dye plasma solutions remains at 900 mμ

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# Computer interpretation of electrocardiograms

*L F Staples M D**
*J E Gustafson M D*
*G J Balm M S*
*W A Tate B A*
*Des Moines Iowa*

The use of the digital computer in the interpretation of electrocardiograms can be a valuable tool especially to the noncardiologist physician Physicians in general practice or those who practice general medicine often read an insufficient number of electrocardiograms to keep all of the salient diagnostic criteria at hand and ready for use

The computer program once stored in the computer is retrieved unerringly and as often as is requested and all quantitative aspects of the electrocardiogram are analyzed The results are consistent and the computer is uninfluenced by anything other than the stored criteria The physician is influenced by what is seen and on occasion may not see a second or third abnormality present and this is especially likely if the first one seen is of some magnitude An example of this is shown in Fig 1 Here it is obvious that the patient has an arrhythmia and that he has had a recent anteroseptal myocardial infarction These were not missed by any of the physicians who read the tracing as an unknown but three of six physicians failed to note the changes of a posterior myocardial infarction as well The computer diagnosed all three abnormalities (Fig 2)

As part of a program designed to demonstrate the usefulness of the computer as an aid to diagnosis a 3 year project was undertaken to write a workable program test its validity and establish its usefulness in a private nonuniversity hospital

## Methods and material

Initially reasonable criteria for the various electrocardiographic abnormalities commonly encountered in adults were selected Programs were written to include all major abnormalities except certain of the arrhythmias Electrocardiograms exemplifying these were selected and technicians were instructed how to measure exactly the various components of the tracings Guidelines outlining the details of measurement were formulated and put into pamphlet form so that technicians could repeatedly refer to them in the interest of standardization in the handling of data

As an example the onset of the intrinsicoid deflection in Lead $V_6$ is measured from the onset of the QRS complex to the point at which the stylus begins to fall abruptly toward the isoelectric line (Fig 3)

Measurement cards (Fig 4) were then completed by the technicians for each

From the Cardiovascular Laboratory [illegible] Iowa Methodist Hospital Des Moines Iowa
This project was financially supported by The John Hartford Foundation Research Number R 14
Received for publication Dec. 14, 1964
*Address Iowa Methodist Hospital 1200 Pleasant St. Des Moines Iowa [illegible]

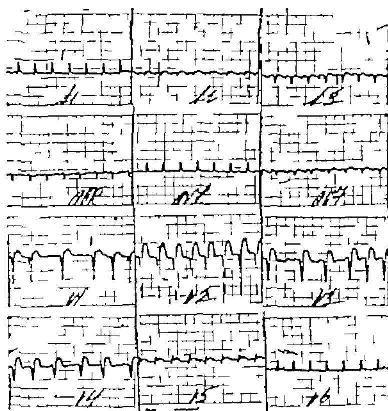


Fig. 1 See text

**IOWA METHODIST HOSPITAL**
RAYMOND BLANK MEMORIAL HOSPITAL FOR CHILDREN
YOUNKERS MEMORIAL REHABILITATION CENTER
ELECTROCARDIOGRAPH (COMPUTER) INTERPRETATION

[redacted] [redacted] 02 19-62 AECG

75 015R

167 X

X

014 X

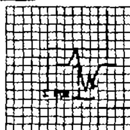
X

X

Fig. 2 See text

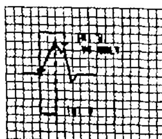
All duration [illegible] are to the nearest [illegible] with the exception of [illegible] [illegible]

[illegible]



QRS [illegible] from the beginning of the complex to its termination

ONSET OF INTRINSICOID DEFLECTION (VENTRICULAR ACTIVATION TIME) [illegible]



[illegible]

Fig 3 See text

tracing IBM cards were punched with four being required for each electrocardiogram as is indicated in the left hand margin of Fig 4 One 90-column card (Fig 5) is punched for the patient's name the date on which the tracing was taken the patient's age the hospital number and the research number A second card is punched with data for heart rate rhythm and P R and Q T intervals and with amplitude measurements for complexes in the standard and augmented leads A third card includes data for the precordial leads through V and a fourth card includes the remaining precordial leads These cards are then ready to be used as data input

The minimum machine requirements for running the electrocardiographic program in its present form includes one of each of the following IBM 1441 Central Processing Unit with 8 000 character storage area 1443 printer 1447 console and a 1442 reader or reader punch

The computer operation of the program must be implemented by placing the standard forms used (Fig 3) on the printer Cards containing program logic are loaded into storage and the computer is now ready to process patient data cards The output will be printed line by line dependent upon interpretations and need not be monitored

A schematic outlining computer logic sequence is seen in Fig 6 Each electrocardiogram is checked by the computer

1 NAME ________ DATE 10-8 AGE 73 H# 83 490 R# OLSR MTH

2
II
R R [illegible] [illegible] 0 RATE 1 4 [illegible] P FREQ 0 1 P DUR [illegible] 4 PR INT 0 [illegible] QT DUR 10 [illegible] 0
P Q R R' S S DUR QRS T T DIPH ST

I [illegible] [illegible] 0 [illegible] 0 [illegible] [illegible] [illegible] 0 [illegible] 0 0 0 [illegible] P P [illegible] [illegible] [illegible]
II [illegible] [illegible] [illegible] 1 [illegible] 1 [illegible] [illegible] [illegible] [illegible] [illegible] [illegible]
III [illegible] 4 0 [illegible] 0 0 [illegible] [illegible] [illegible] [illegible]
AVR [illegible] [illegible] 0 1 0 [illegible] 0 [illegible]
AVL 0 [illegible] [illegible] [illegible] 0 [illegible] [illegible] [illegible] [illegible] 0
AVF [illegible] [illegible] [illegible] [illegible] 0 0 [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] INT D

3
V1 [illegible] [illegible] 1 4 0 [illegible] 0 0 1 4 [illegible] 7 [illegible] 1 [illegible] [illegible] [illegible] [illegible]
V [illegible] [illegible] [illegible] [illegible] [illegible] 0 0 [illegible] 0 [illegible] 0 0 1 [illegible] [illegible] [illegible] [illegible] [illegible]
V3 1 [illegible] 0 [illegible] [illegible] [illegible] [illegible] [illegible] 1 [illegible] [illegible]
V4 0 7 [illegible] [illegible] 0 [illegible] [illegible] 0 [illegible] 1 [illegible] 0

4
V5 [illegible] [illegible] [illegible] [illegible] [illegible] 1 1 [illegible] [illegible] [illegible] 1 [illegible] [illegible] 4 [illegible]
V6 0 [illegible] 0 [illegible] [illegible] [illegible] [illegible] 0 [illegible] 7 [illegible] [illegible] [illegible] 0 [illegible] [illegible] [illegible] 4 [illegible]

Fig 4 See text

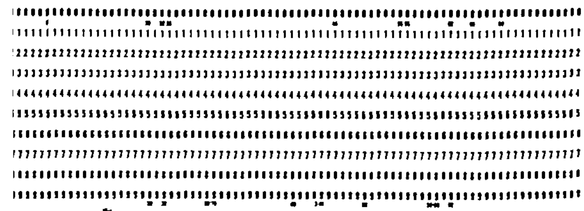


Fig 5 See text

for patient data (name hospital number research number etc) and then for electrocardiographic data beginning with the heart rate (calculated from R R interval unless the rhythm is not regular in which case the rate has been measured by the technician counting R waves in a 3 second interval) The computer converts the R R interval to heart rate by the equation

$$HR = \frac{60}{(\text{R R interval in sec})}$$

The P R interval QRS duration and the presence or absence of arrhythmia WPW syndrome complete RBBB complete LBBB or an intraventricular conduction defect are next considered Following these RVH LVH Q T (corrected for rate) posterior myocardial infarction (evolutionary acute old and probable in that order) and anterior myocardial infarction (acute evolutionary and old in this order) are checked for Last of all T wave changes (abnormal or borderline)

## AECG GENERAL LOGIC FLOW

READ I
P T

PRINT
IDENTIFICATION

PUT LAR ER DURA ON
OF QRS Y OR $V_6$ — ON

QRS VOL
YF

DOR 6 X
04 SEC

S RHYTHM
REGULAR

NO

PUT RATE —
20 WAVES
TO SQUARES

YES

PUT RATE =
60 / R SEC

WRITE
RATE

YES

RHYTHM
REGULAR

NO

EVENT

YES

WRITE
RHYTHM

CHECK APPROPRIATE
LEVEL
ACHYCARD

ATRIAL
FIBRILLATION

YES

EVENT

NO

WRITE
ARRHYTHMIA

YES

YES

INTERVAL
= 0

INTERV
TO ECK APPROP
LEVEL BLOCK

CHECK
(SLOPE)

NO

CHECK OR

ES

PRES

YES

NO

YES

>0 11

NO

<4 mm

NO

ECK
RTH

CHECK

CD

RH

NO

ES

QT CORRECT

CH
ON
LONG
SEN

LONG
EVENT

NO

ES

CHECK
CT ON

PROBABLE OR
TE LVH
CLUES OR
CT

YES

NO

CH
CR
T

STAR EX

Fig. 4 See text

and S-T segment changes (abnormal or borderline) are searched for in the order indicated. The latter are omitted in the presence of bundle branch block or ventricular hypertrophy. Complete RBBB and complete LBBB are mutually exclusive and if either is diagnosed as being present RVH and LVH are not considered for purposes of this program.

In an effort to evaluate and validate the program currently in use in the computer 145 electrocardiograms considered to be reasonably typical examples of normal and abnormal tracings commonly encountered and which have been programmed were sent as unknowns to two university cardiologists and to six other internists.

Table 1 lists the tracings in which a significant difference of opinion existed between readers and the computer. Much of this is due to overreading or to underreading by the computer.

The six nonuniversity internists had major differences in diagnoses varying from thirty four instances per physician with the average difference being sixteen.

**Results**

Four thousand four hundred and sixty nine electrocardiograms have been analyzed by the computer. Each computer diagnosis was checked by one of the authors (E. L. S.) and each of the cardiograms was read by him in order to check computer accuracy. His diagnosis and that of the computer were in agreement except for nineteen electrocardiograms. Thirteen of these were considered to have been overread by the computer as posterior infarction and two as anterior infarction. In so far as has been possible consecutive electrocardiograms taken on patients make up the above number. Because duplicate copies of the electrocardiograms were not made for all patients some were lost to

*Table 1*

| *Tracing number* | *Computer diagnosis* | *Physicians' diagnosis* |
|---|---|---|
| 11 | Complete right bundle branch block | Right ventricular hypertrophy |
| 17 | Anterior infarction and posterior infarction | Anterior infarction |
| *03R* | *Complete right bundle branch block and posterior infarction* | *Complete right bundle branch block* |
| 10R | Left ventricular hypertrophy and anterior infarction | Left ventricular hypertrophy anterior infarction posterior infarction |
| 15R | Arrhythmia anterior infarction posterior infarction | Atrial fibrillation anterior infarction |
| 22R | Left ventricular hypertrophy anterior infarction posterior infarction | Anterior infarction and posterior infarction |
| 23R | Anterior infarction posterior infarction | Anterior infarction |
| 25R | Left ventricular hypertrophy anterior infarction | Left ventricular hypertrophy |
| 50R | Atrial fibrillation right ventricular hypertrophy posterior infarction | Atrial fibrillation right ventricular hypertrophy |
| 57R | Left ventricular hypertrophy anterior infarction | Left ventricular hypertrophy |
| 60R | Left ventricular hypertrophy anterior infarction | Anterior infarction |
| 102R | Right ventricular hypertrophy posterior infarction | Incomplete right bundle branch block |
| 104R | T and S-T abnormal | Anterior infarction |
| 108R | T abnormal | Posterior infarction |
| 111R | Anterior infarction posterior infarction | Anterior infarction |
| 114R | Left ventricular hypertrophy anterior infarction | Left ventricular hypertrophy |
| 126R | Right ventricular hypertrophy posterior infarction | Posterior infarction |
| 145R | Atrial fibrillation posterior infarction | Atrial fibrillation left ventricular hypertrophy posterior infarction |

*Table II Computer diagnosis of 4 469 electrocardiograms*

| Number of tracings | Diagnosis | Number of tracings | Diagnosis |
|---|---|---|---|
| 469 | Normal | 1244 | Within normal limits |
| 157 | Tachycardias | 1334 | Abnormal T waves |
| 861 | Abnormal S-T segments | 238 | Atrial fibrillation |
| 10 | 2nd or 3rd degree A V block | 5 | Wolff Parkinson White syndrome |
| 164 | 1st degree A V block | 71 | Short P R interval |
| 32 | Intraventricular conduction defect | 373 | Prolonged Q-T interval |
| Ventricular Hypertrophy | | | |
| 9 | Right | 93 | Left |
| 39 | Possible | 171 | Possible |
| 9 | Probable | 77 | Probable |
| Bundle Branch Block | | | |
| 116 | Complete right | 89 | Complete left |
| 34 | Incomplete right | | |
| Myocardial Infarction | | | |
| | *Posterior (diaphragmatic)* | | *Anterior* |
| 21 | Acute | 36 | Acute |
| 42 | Evolutionary | 61 | Evolutionary |
| 254 | Old | 268 | Old |
| 78 | With lateral extension | | |

the project However the tracings taken are considered to be representative of a cross section of those taken in a large general hospital population with acute conditions Table II shows the distribution of the diagnoses as printed by the computer

Within normal limits includes tracings with minimal tachycardia bradycardia minimal prolongation of the P R interval borderline Q T interval borderline T wave and borderline S-T segment changes if these were the only diagnoses made on the tracings Second degree and third degree A V blocks were diagnosed categorically when the atrial (P wave) rate was more rapid than the ventricular (QRS) rate (premature atrial contractions excepted) No attempt was made to separate second degree from third degree A V block in this program

Posterior infarction with lateral extension was diagnosed whenever in addition to Leads II III and aVF appropriate changes were also seen in Leads V[illegible] and V[illegible]

In 155 tracings abnormalities of the T wave only were diagnosed and in only 20 cases was the diagnosis abnormal S-T segment only In 151 electrocardiograms the combination of abnormal T wave and S-T segment only was diagnosed

## Comments

In a very short time after the start of the project it became apparent that changes had to be made in the manner in which usual criteria were handled in order to adapt them to a computer program Criteria are weighted in formulas which can be adjusted to correct for underreading or overreading a particular abnormality

As an example the left ventricular hypertrophy program assigns varying weight to the R wave amplitude in Lead V[illegible] or Lead V[illegible] Lead aVL or Lead aV[illegible] and to the T wave in Lead V[illegible] the latter being influenced also by the amplitude of the R wave in Lead $V_6$ Weight is also given to a negative S T segment A scale is set up and in terms of the sum of the product from each of the formulas a decision is made whether left ventricular hypertrophy is or is not present and if it is whether it is possible probable or definite (marked) (Fig 7) Similar formulas are used in deciding on the presence or absence of right ventricular hyper

```
Page 3  APCG

VII  V tri  lar hypertrophy (Don't check [illegible] or [illegible] if [illegible] or [illegible] is present)

     A  Left
        1  ([illegible] 1[illegible])4 or ([illegible] [illegible])4 (Use greater of 2 products)
        2  ([illegible] [illegible])2
        3  (Intrinsicoid [illegible]  [illegible]) (10[illegible]) ([illegible])
        4  ( 1 [illegible]  T[illegible]) ( [illegible]) ([illegible]) (If T[illegible] <-2 make it = -2)
        5  ([illegible] VL  1[illegible])3
        6  ([illegible]  2[illegible])3
        7  ( 1 [illegible]  [illegible]) ( 2) ([illegible]) (Only if [illegible] and [illegible] are > 1[illegible])
        8  ([illegible]  [illegible]) (If [illegible] < [illegible])

     B  Criteri
```

| AGE | [illegible] | POS[illegible] LE | PRO[illegible] [illegible] | [illegible] |
|---|---|---|---|---|
| > 33 | [illegible] 49 | [illegible] 7[illegible] | 71 [illegible] | > [illegible] |
| ≤ 33 | 4[illegible] [illegible] | [illegible] [illegible] | [illegible] 100 | > 100 |

Fig 7 See text

trophy complete and incomplete right bundle branch block and complete left bundle branch block A cardiologist who wishes to emphasize amplitudes of R waves or to make the program more sensitive may simply change a factor in the appropriate formula

Myocardial infarctions are handled through generally accepted criteria The electrocardiographic age of an infarct is determined by S T segment elevation and by the depth of T wave inversion It is recognized that this can at best be an approximation since serial comparison is not performed in the present program Old posterior infarctions have given considerable difficulty because of the absence of clear cut criteria especially in low voltage tracings

One of the drawbacks of the program in its present form is that a considerable amount of time must be spent in teaching technicians to do the measurements properly Also a skilled technician requires on the average 10 minutes to make the appropriate measurements These must then be transferred to cards as indicated earlier The total time required to completely process each electrocardiogram including a printed diagnosis from the computer is about 11 minutes In order to circumvent measurement by a technician and to shorten the time required for processing and in order to make possible direct transmission of analogue data to the computer an FM tape program is presently in the developmental stage

## Summary

The use of the digital computer in the interpretation of electrocardiograms seems to offer assistance especially to the non cardiologist physician To test this thesis a 3 year project was undertaken to write a workable program test its validity and establish its usefulness in a private non university hospital This paper presents the factors involved in the programming and the problems encountered

Our experience indicates that computer interpretation of electrocardiograms is successful Although the input of most of our material has been from hand measurements by a technician the program also works on electronically converted data

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# Coronary inflow after systemic-to-coronary artery anastomosis in dogs

*Hans H. Schaldt, M.D.**
*Harm Krause, Ph.D.*
*Berlin, Germany*

Because of the fact that the morbidity and mortality of stenosing coronary diseases recorded in the statistics on heart troubles have been increasing at an alarming rate in almost all industrialized countries since World War II, therapy research in this field has been intensified during the last decade. Since the prerequisites for a coronary dilating collateral circulation inducing effect by drugs are mostly limited in the case of advanced structural lesions of the walls with a reduced flexibility and high-grade narrowing, the demand for adequate surgical measures to be applied to such patients is becoming more urgent.

Whereas *indirect* methods for the revascularization of the ischemic myocardium, such as cardiopexy with extracardiac structures containing vessels, hyperemization of the cardiac surface by producing a sterile epicarditis, arterialization of the coronary venous system, implantation of the internal mammary artery into the myocardium, or bilateral ligature of the latter, have not yet yielded any convincing results in animal experiments and in clinical practice, *direct* surgical interventions on the coronary arteries appear to promise more success in so far as the segmental stenoses of main branches are concerned. In addition to efforts made toward removing stenoses of the lumen by curettage, endarterectomy, and dilation of the stenotic ring by means of a patch graft, numerous experiments have been aimed at overcoming the segmental narrowing by creating an anastomosis between an arterial branch of the arotic arch and the coronary stem beyond the stenosis. The shunting was made via mobilized arteries,[1-7] arterial or venous vascular grafts,[2,4,8,10,12,13] or prosthetic vessels.[3,4] Although such experiments have partially led to satisfactory laboratory results, a clinical application has hitherto been condemned to failure because of the high percentage of thromboses occurring in the vascular shunts of small caliber. This may well account for the fact that so far experimenters in this field have almost invariably confined themselves to the surgical problem of the suturing technique to be applied, whereas the functional behavior of anastomoses was dealt with merely in a general clinical respect. Thus no publication yet exists which describes the peculiar hemodynamic conditions in systemic-to-coronary artery anastomoses.

This paper reports on experiments in which the coronary inflow in dog hearts was examined prior to and after the shunting with systemic arteries.

Received for publication Dec. 16, 1963.
Address: Department of Experimental Cardiac and Vascular Surgery, German Academy of Sciences, Hospital am Friedrichshain, Berlin 1017, Germany.

**Methods**

The studies were performed on 25 mongrel dogs weighing 24 to 28 kilograms. Morphine was applied as a preanesthetic and anesthesia was induced with sodium barbital (approximately 30 mg. per kilogram). The respiration was maintained by means of a mechanical insufflator via a cuffed endotracheal tube using fresh air. The thorax was opened in the fifth left intercostal space with the animal on its right side. After the pericardium had been opened above the auriculoventricular sulcus, the circumflex branch of the left coronary artery was exposed from its origin to the site of branching of the ramus marginis obtusi anterior. This resulted in a segment of about 4 cm. in length which was freed from small tributaries as well as from the ramus descendens ventriculi sinistri. If the latter was of large size, which would have meant the formation of an extensive area of infarction, the animal was used for other experimental purposes. The main branch to the septum and the proximal auricular branch were carefully spared. The coronary anastomosis was performed with the left subclavian artery mobilized directly or via the left internal mammary artery or a rubber tube having a 3 mm. inner diameter which was joined with the left subclavian artery at the site of branching of the mammary artery via a short prosthetic tube of the same diameter. The wall of this model vascular tube was shaped in such a fashion that in the coronary region of measurement identical formal criteria of the pressure and flow pulses were fulfilled as in shunting with the subclavian artery or mammary artery, so that similar volume elastic effects could be assumed in the arterial pressure region. After the vessels selected had been dissected free, the dog was heparinized intravenously in order to maintain a constant level (initial dose 5 mg. per kilogram).

The anastomosis was applied to the normally beating heart, using a thin-walled brass tube, the diameter of which was adapted to the smallest of the two shunting vessels (varying in these experiments between 2.2 and 3 mm.) and the length of which was 18 mm. This tube served at the same time for both pressure and flow measurements according to the differential pressure method. For this purpose it was provided with two lateral pipes 0.8 mm. in diameter and 10 mm. in length, which were attached 8 to 10 mm. apart and connected each with the measuring chamber of Statham P 23Gb transducers via flexible inelastic tubes. The transmission of pressure from the blood channel to the recipient membranes of the strain gauges was thus accomplished through the lateral pipes, the inelastic tubes, and the measuring chambers of the transducers; this system was filled with physiologic saline free of bubbles. With the given diameters of the measuring tubes, the distance of 8 to 10 mm. between the pipes was sufficient to obtain measurable pressure differentials with arterial blood speeds. The pressure differentiation was accomplished by compensation of the two Statham transducers, which were of similar pressure sensitivity. The flow zero was determined mechanically by means of two three-way stopcocks which were arranged between the inelastic tubes and the measuring chambers, and which could be changed over in such a way that the strain gauges became adjusted to atmospheric pressure and the column of fluid between the blood channel and the transducer was simultaneously interrupted. The natural frequency of the manometric system amounted to 500 c.p.s.

Since the pressure and inflow conditions of the left circumflex artery had to be examined alternatively for comparison under original and extracardiac blood supply, the anastomosing measuring tube had to be shaped in such a manner that it could connect the peripheral portion of the coronary artery with both the central portion and the systemic shunting vessel. The measuring tube used consisted of two parts, each provided with a lateral pipe and fitted into one another by means of a gap-less joint. The two parts when fitted together formed the measuring tube of the above stated dimensions. The central component tube existed in duplicate, one being inserted into the extracardiac shunting vessel and the other into the central portion of the coronary artery. Thus it was possible to adjust the pathway of the coronary blood supply as desired by a simple plugging over of the peripheral component tube to one of the two others: the free supply artery was

clamped during this time. Particular care had to be taken that the measuring tube was always in a horizontal position on the surface of the heart.

In order to minimize the time of interruption of blood flow when the tubes were being joined, the composite measuring tube was at first connected with the extracardiac vessel. Then the circumflex branch was ligated in two places in the middle third of the mobilized distance and was intersected between these, and the free end of the measuring tube was inserted into the peripheral stump. In general, this procedure took no more than 60 seconds. Finally, the remaining central component tube could be inserted easily into the clamped central stump of the circumflex branch.

In addition to the absolute and differential coronary pressure, the pressure of the left ventricle, that of the aortic bulb, and that of the coronary sinus were optically recorded via puncturing needles or short catheters which were inserted intrathoracically.

Since the relationship between speed and pressure differentials is not the same in phasic flows as in stationary ones, a gauging under dynamic conditions was necessary. For this purpose we used an artificial partial circulatory system which permitted simulation of the hemodynamic situations of the arterial system and, in addition, the recording of outflow measurements. This arrangement produced a pulsating flow, the amplitude, shape, and time course of which were similar to the original coronary flow pulse of the tested animal. Gauging was based on the relationship between the integral of the recorded flow curve and the outflow of blood during the registration. Since the measurement of the differential pressure is particularly sensitive in response to changes in viscosity, gauging was carried out immediately after the experiment with the arterial blood of the still living dog.

## Critique of methodology

In so far as the determination of the phasic flow of heterogeneous fluids from the static differential pressure is concerned, neither a generally valid theory nor any physical experiments exist from which the expected precision of measurement can be calculated. The respective theoretical considerations are based on the fundamental equations of hydrodynamics according to Euler (1755) and Navier-Stocke (1845), the former referring to ideal fluids, the latter to viscous fluids. Frank[3] developed his functional equations for measuring the differential pressure from Euler's fundamental equations, whereas the equations formulated by Navier-Stocke led to the Hagen-Poiseuille law which is valid for stationary flows in rigid tubes. Thus these equations represent but starting points for the complicated case of measuring the phasic flow of viscous fluids from the differential pressure. Therefore, this method can be judged only empirically at present. In agreement with Gregg and his associates,[? ?] we were able to conclude from comparative measurements in the laboratory, using electromagnetic flow meters, that a sufficient time resolving power and an acceptable reproduction of the amplitudes can be achieved, although this measuring and gauging method does not give absolute evidence of the actual flow conditions. For the present experiments the measurement of the differential pressure, as opposed to the electromagnetic method, offered the advantage of simultaneous recording of the flow and pressure pulses in the same area of blood flow.

Since the internal cross section of the measuring tube correspond to the lumen of the shunting vessels, no essential dynamic repercussions on local circulation can arise. In order to prevent inflow disturbances, the arterial inflow and outflow distances must be located in one and the same straight line. With extracardiac blood sources in the region of the aortic arch this is only possible if the circumflex branch of the left coronary artery is shunted (see Fig. 1).

[illegible]



Fig. 1. Angiographs of a dog with coronary anastomoses between the left mammary artery and the left circumflex artery (←) as well as between the right mammary artery and the anterior descending artery (→) using polyethylene prosthetic rings. The control examination was performed on the regularly beating heart 8 months after the operation. The left arteriogram shows a retrograde filling of the right coronary artery.




Fig. 2. Original curves of pressure and flow of systemic to left circumflex artery anastomoses with low flow resistance (*A*) and high flow resistance (*B*, *C*). (*For details see text.*) Indicated time interval is 100 msec.

**Results**

Fig. 2 reproduces original curves of pressure and flow of anastomoses applied between the subclavian artery (*A*) or the internal mammary artery (*B*, *C*) and the left circumflex branch. To label the differences as compared to the original pressure and flow curves of the coronary artery concerned, the equilibrated coronary oscillations which had been recorded immediately before or after shunting or during the latter—the respiration as shallow as possible—and which showed congruent pressure curves of the left ventricle have been synoptically demonstrated in Fig. 3. As is shown by the prototype curve segments in *A*, after retardation of the anastomotic pulse wave, as compared to the onset of ventricular ejection, the throttling of the early systolic inflow as well as the mid systolic forward flow are increased. After the maximum systolic flow had been reached, the anastomotic coronary pressure rises above the ventricular pressure. At the same time, the speed abruptly decreases. Coincident with the




Fig 3 Reproduction and comparison of original pressure and flow curves recorded prior to and after application of systemic to-left circumflex artery anastomoses having a sufficient (*A*) and a too narrow (*C*) lumen *Black areas* Anastomotic additional inflow *Hatched areas* Loss of anastomotic flow as compared to the normal coronary inflow

closure of the aortic valves and onset of isometric relaxation an acceleration of flow as well as a decline in pressure are to be recorded during the anastomotic coronary main wave Along with the onset of the anastomotic dicrotic wave we observed a second acceleration of blood lasting longer than the preceding one and leading to a stronger diastolic initial filling of the coronary artery In the further process of diastole both pressure and flow curves that were recorded became approximately similar to each other

In order to permit a better understanding of curves *B* and *C* of Fig 2 we should like to explain these changes in pressure and flow first of all on the basis of the hemodynamic interrelationship between the pulse wave of the systemic artery which is transported to the left ventricle on a detour the starting pulse in the aorta and the changes in peripheral resistance in the myocardial cycle Since the final diastolic pressure of the extracardiac anastomosis is reached only during the output period an increasing pressure gradient from the aorta to the coronary artery is recorded upon the onset of ejection from the left ventricle This gradient counteracts the deceleration in flow of early systole which is favored by the long and elastic vascular tube of the anastomosis and moreover effects an additional acceleration of blood upon arrival of the anastomotic main wave Upon discontinuance of the accelerating effect of the gradient at the point of intersection of ventricular or aortic pressure and anastomotic pressure the high speed is suddenly discontinued too This in turn leads to a further rise in pressure since the flow pressure acts as an additional static pressure right here The inversion of the aorto-coronary pressure incline resulting therefrom leads to a brusque diminution in flow The subsequent myocardial relaxation starts prior to the end of the anastomotic coronary main wave Since the blood flow of the shunt artery is slowed down at this time only a partial volume can be accelerated with a simultaneous drop in pressure The retarded dicrotic wave meets this partial volume Thus the volume is accelerated twice The efficiency of this acceleration is diminished however by the fact that a centripetal pressure gradient exists between the aorta and the coronary artery even during protodiastole This leads to an approximation of the anastomotic and original coronary inflow volumes already existing in mid-diastole

These mechanism of an increased initial filling can however become effective only if the resistance of the shunt vessels is small enough to supply the quantity of blood required within the shortest possible interval Such a prerequisite does not exist in experiments *B* and *C* of Figs 2 and 3 Whereas only a moderate delay of the inflow is demonstrated in *B* the curve segments in *C* show a considerable insufficiency of the anastomotic volume capacity with a strong decline in pressure in early diastole

So as to be able to estimate the influence of the distance of the shunt pathway upon coronary inflow, the planimetry values of the anastomotic flow curves and the corresponding time values of the aorto-coronary pulse retardation ascertained by 74 individual measurements made in 6 suitable dogs were put into relationship with one another. Three of these animals belonged to an experimental series in which the model vascular tube with an internal diameter of 3 mm. was inserted between the origin of the left internal mammary artery and the left circumflex branch, being systematically shortened after each double measurement. The other 3 dogs were taken from a second experimental group in which analogous measurements were made. Here the mammary artery served as the shunt vessel. As for the physical parameters which may spontaneously change the coronary inflow in the reproduction experiments having a regular supply of oxygen to the myocardium, these above all had to be approximately constant: the aortic and coronary venous pressure, the systolic and diastolic inflow periods, the coronary inflow under natural conditions, as well as the coronary resistance, which can be estimated from the mean diastolic aortic pressure minus the critical closing pressure, and the myocardial circulation per minute per 100 grams.[4] The mean duration of a cardiac cycle approximated 523 msec. (± 3.8 per cent). The diastolic aortic pressure effective for the coronary perfusion ranged from 75 to 79 mm. Hg, with amplitudes from 37 to 42 mm. Hg. The mean coronary sinus pressure amounted to 8.8 mm. Hg ± 9 per cent (max.) or 2.1 mm. Hg ± 28 per cent (min.), respectively, under natural arterial inflow conditions, so as to partly rise again after application of the anastomosis. (The behavior of the coronary venous blood flow in the case of extracardiac anastomoses is now being investigated in detail.)

The time-volume relationships of the anastomoses with the model vascular tubes (*a*) and with the mammary artery (*b*) are graphically demonstrated in Fig. 4. The ordinates state the percentage surface difference as compared to the original coronary flow curve; this comparative value is assumed to amount to 100 per cent. It turned out that in both experimental groups the systolic inflow was relatively more strongly affected by retardation of the anastomotic pulse wave than by the diastolic blood flow. Because of the considerable acceleration of blood in mid-systole the blood flow recorded during the output period in the tubes amounted to a pulse lag of 55 msec., and in the narrow-lumen arteries pulse lags of 36 to 43 msec. above the corresponding coronary value. Only after these times have been exceeded does the prolonged duration of the early systolic throttling of the blood flow have a

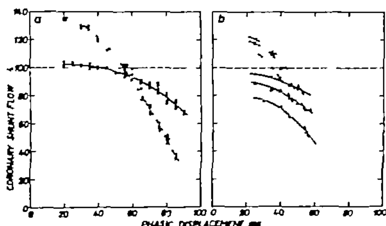



Fig. 4. Graph indicating as percentage the changes in flow of coronary-to-systemic artery anastomoses in systole (*dashed lines*) and in diastole (*solid lines*) with different phase displacement between the pulse waves of the aorta and those of the coronary artery. *a*, Anastomoses with low flow resistance. *b*, Anastomoses with high flow resistance.

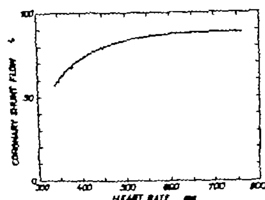



Fig 5 Diagram on the relative changes in flow of an extracardiac coronary anastomosis with a too small diameter at a varying heart rate

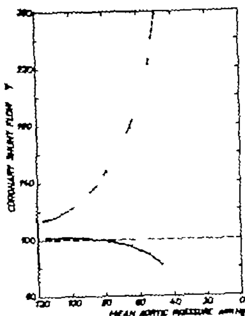



Fig 6 Opposite changes in the systolic (upper curve) and in the diastolic (lower curve) coronary inflow with a decline in the aortic pressure Phase angle 22 degrees

more significant effect and finally become preponderant in an exponential ratio In diastole the twofold acceleration of blood may lead to a slightly increased inflow under conditions of a minor lag and a sufficient cross section despite the retardation of the second rise If the time difference exceeds 42 msec an exponential diminution in flow is recorded If the cross section is too narrow above all the diastolic flow in long shunt pathways is considerably reduced

The diagram of Fig 5 illustrates the dependence on frequency of the anastomotic blood flow with an insufficient cross section of the shunt artery The changes in frequency have been thermically effected by cooling and heating of the sinoatrial node In the graph the surface values of the total coronary inflow recorded prior to and after application of the shunt under conditions of adequate cardiac cycles (after a steady state has been established) are compared with regard to their percentage With a rise in frequency the increase in the difference in flow recorded in the physiologic range is relatively insignificant Only at a higher stroke rate does this difference in flow increase more markedly This results in a prolonged systolic period per minute and a corresponding decrease in diastole The diastolic ventricular pressure and the coronary sinus pressure did not undergo any significant change

Finally the inflow of a mammary coronary anastomosis with a sufficient anastomotic volume capacity under conditions of physiologic pressure and frequency was examined in analogous comparative measurements with a spontaneous decline in the aortic pressure This situation arises in prolonged experiments when the development of pressure in the heart is finally reduced because of myocardial fatigue As a consequence the early systolic throttling of the blood flow is decreased while a relative increase in the mid systolic forward flow is recorded Upon a more marked decline in pressure we observed a considerable drop in diastolic blood flow This shifting with regard to the relationship between systolic and diastolic inflow in favor of systole is demonstrated in Fig 6

**Discussion**

As is shown by the values recorded the blood flow of a systemic artery that is shunted to the heart is subject to phasic changes similar to those of blood flow in the coronary artery Basic differences at the beginning of the systolic and diastolic inflow can be analyzed from the lag between the pulsatile blood supply and the rhythmic changes in coronary resistance They are quantitatively influenced by the degree of the phase angle of the anasto

motic pulse wave as compared to the contraction cycle of the left ventricle as well as by the formation of alternating aorto-coronary pressure gradients. In systole the phase-dependent delay in filling is overcompensated by a strongly blood-accelerating anastomotic pressure gradient, thus being associated with a high pressure and flow load of the shunting vessels. The increase in diastolic inflow arising from the volume acceleration effected twice is more favorable in a hemodynamic respect. Both factors may increase the total coronary inflow under given mechanical conditions. This respective observation is in agreement with the results published by Lord and co-workers.[22] At the time of comparative measurements of the coronary venous outflow prior to and right after the application of a subclavian to coronary artery anastomosis they obtained higher values in the case of shunting.

The length of the extracardiac shunt pathway is of decisive importance for the coronary inflow rate. The ventriculo-coronary phase angle as well as the flow resistance in the vessels of small caliber depend on this distance. If the cross section is big enough, a prolongation of the bypath leads to an exponential decrease in the systolic and diastolic inflow due to the increasing delay of initial filling. This effect of a time-condition deficient inflow is intensified by a resistance-induced filling insufficiency in the case of vascular lumina which are too narrow.

This combined flow-inhibiting effect was observed in most cases of anastomosis of a coronary artery with the internal mammary artery, which is preferably used by the experimenters[1,7] because of its location near the heart, adequate size, and replacement by way of collateral vessels. Notwithstanding this fact, the functional behavior of such shunts in surviving animals has so far been described as being sufficient. Here the angiographic detection of the anastomosis, the absence of symptoms of hypoxemia in the electrocardiogram, and the maintenance of a normal exercise tolerance have served as evidence of a sufficient myocardial perfusion in the anastomotic region.[11,16,19] We are able to confirm these clinical findings even after the application of a stenosing nonsuture technique with rigid rings. However, as has been proved by radiographic checks and postmortem vascular visualization, the decreased supply of coronary blood is compensated for by intercoronary anastomoses (Fig. 1). Obviously, the development of a functionally efficient collateral circulation can be promoted by regular physical loading of the dogs. As may be seen from the symptomatic curves of Figs. 5 and 6, the inflow from the mammary artery anastomoses may drop to critical values in the acute experiment if a stronger increase in frequency or a drop in the arterial systemic pressure is recorded.

When judging the respective results, one must give due consideration to the fact that the phase pressure and flow courses were demonstrated on mobilized coronary branches located on the myocardial surface and thus were affected by pendulum oscillation of the pulse waves and volume-elastic changes in vascular capacity. We think, however, that the results are of comparative value with reference to the actual intramural flow conditions. Although the relatively wide lumen anastomoses with the subclavian artery may equal or even exceed the original reference data with pulse lags up to about 40 msec., the underlying compensating mechanisms constitute over a longer time period a dangerous vascular load and are thus in fact unphysiologic. It is also presumable that the considerable prolongation of the coronary inflow tract leads to an increasing danger of thrombosis because of the higher vascular resistance. Therefore, an artificially changed coronary blood supply can be economical only if the surgeon endeavors to create the shortest possible external circulatory system. This had already been attempted in 1957 by Julian and associates[4] and later by Daicoff and associates[3] and DeBakey,[14] who implanted a short homologous artery graft or prosthetic vessel between the ascending aorta, 2 to 3 cm. above the valve, and the main branches of the coronary artery.


## Summary

In acute experiments with thoracotomized dogs we determined the inflow into the circumflex branch of the left coronary artery by comparison under original flow

conditions and after anastomosing with systemic arteries of varying length and cross section using the left subclavian artery, the left internal mammary artery or in lieu of the latter model vascular tubes with similar elastic properties.

As has been proved, the prolonged path way of the coronary pulse wave and the resistant and accelerative forces of the left ventricle lead to both a systolic and a diastolic initial deficiency of filling and to a subsequent additional inflow as compared to the natural coronary flow. Provided that the cross section of the extracardiac shunting vessel is sufficient, the algebraic difference between both values depends on the degree of the phase displacement between the onset of the ventricular output period and the arrival of the coronary pulse wave on a detour. In the present experiments the ventriculo coronary or aorto coronary phase angle required for an adequate systemic-to-coronary artery inflow was below 38 degrees (5 msec.) for systole and below 29 degrees (42 msec.) for diastole. When these values are exceeded, the inflow drops in the shape of an exponential function.

When the internal diameter of the extracardiac shunting vessel was too small (below ca. 2.5 mm.), then the mid systolic and protodiastolic inflows were reduced even with the shortest possible bypath between the subclavian artery and the coronary artery, causing a reduction in the total inflow rate in comparison with the natural values. In the chronic experiment the physiologic range of regulation of the coronary system with such anastomoses can, however, be maintained by the formation of compensating collateral channels.

A strong rise in frequency and a spontaneous drop in arterial pressure may lead to a critical insufficiency of flow in the systemic-to-coronary artery anastomoses of small caliber.

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# Case reports

## Cardiac tamponade after transmyocardial extravasation of contrast material

*Manouchehr Nadimi, M.D.**
*Lampis D. Anagnostopoulos, M.D.***
*Martin J. Frank, M.D.****
*Jersey City, N. J.*

Among the various complications that follow angiocardiography are arrhythmias,[1-4] allergic reaction to contrast material,[1,5] hypotension and circulatory collapse,[7] pneumothorax and pleural effusion,[1] pulmonary infarction and parenchymatous changes in the lung,[8] endocardial trauma,[1] perforation of the heart,[1,9] coronary ischemia, occlusion, and myocardial infarction,[1-4,10,11] and extravasation of contrast material into the myocardium or pericardial sac.[1-11,14]

Although extravasation of contrast material into the myocardium or pericardial sac during angiocardiography has been reported by many authors, the outcome of this complication has varied. Cardiac tamponade[12,13] and death[8] have occurred in some patients, whereas others have fully recovered without special treatment.[1,14] Despite the frequency and seriousness of this complication, the cause of tamponade and the factors responsible for a variable outcome have not yet been investigated. The purpose of this communication is to report a case in which tamponade occurred after the transmyocardial extravasation of contrast material, to report the result of animal studies performed to investigate the mechanism of tamponade that followed the entry of contrast material into the pericardial sac, and to suggest a program for the management of patients in whom this complication occurs.

### Case report

A 58-year-old white woman was admitted to the Thomas J. White Cardiopulmonary Institute for cardiac catheterization. Physical examination, chest films, and electrocardiogram were compatible with rheumatic heart disease with mitral stenosis, mitral regurgitation, and aortic stenosis. Routine laboratory examinations, including bleeding, clotting, and prothrombin times, were within normal limits. The hematocrit was 40 per cent.

On Oct. 8, 1964, the patient underwent a standard right and retrograde left heart catheterization to demonstrate the severity of the respective valvular lesions. A gradient of 27 mm. Hg was found across the mitral valve and a gradient of 10 mm. across the aortic valve. For demonstration of the severity of mitral regurgitation, cineangiography was performed. At 1:30 P.M., 50 ml. of 85 per cent Hypaque (brand of sodium diatrizoate) was injected into the

From the Department of Medicine, New Jersey College of Medicine and the Thomas J. White Cardiopulmonary Institute, B. S. Pollak Hospital for Chest Diseases, Jersey City, N. J.
This work was supported by grants [illegible] from the United States Public Health Service (HE-[illegible]) [illegible]
Received for publication [illegible] 1965.
*Instructor in Medicine, New Jersey College of Medicine.
**Formerly Fellow, Cardiology, Department of Medicine, New Jersey College of Medicine. Present address: [illegible] Cardiology Department of Medicine, University of Chicago, Chicago, Ill.
***Associate Professor of Medicine, New Jersey College of Medicine. Address: New Jersey College of Medicine, 24 Baldwin Ave., Jersey City, N. J. 07304.

left ventricle through a No 6F NIH catheter by a Gidlund pressure syringe at a pressure of 8 kilograms per square centimeter Immediately after injection the operator noted that approximately 80 per cent of the contrast material had entered the pericardial sac rather than the left ventricle and the patient complained of severe precordial pain Recorded pressures showed a normal left ventricular contour without hypotension Intermittent fluoroscopy over the next 70 minutes revealed gradual expansion of the pericardial space which was well outlined by the contrast material At 2 30 P M the patient became cyanotic and hypotensive with a systolic pressure of 70 mm Hg and pulsus paradoxus Over the next 2 minutes the peripheral pulses became impalpable and the blood pressure unobtainable At 2 32 P M under fluoroscopic guidance n pical pericardiocentesis was performed and 118 ml of bloody fluid was withdrawn The fluid was found to have a hematocrit of only 5 per cent Immediately after the removal of the fluid tal sign returned to normal and the cardiac silhouette became smaller However 40 to 50 per cent of the original amount of estimated pre pericardiocentesis fluid was still visible fluoroscopically No further attempt t piration was made because the patient condition was markedly improved nd ventricular irritability resulted from e contact of the aspirating needle with the myocardium Vit l signs remained normal throughout e ght d a he t x ray film taken the next orning failed to demonstrate residual contrast aterial in the pericardial a

## Comments

A pericardial fluid hematocrit of only per cent appears to indicate that hemor age was not the cause of tamponade in is patient Since Hypaque in the con ntration used has an osmolality in excess 2 500 mOsm per liter whereas plasma molality is approximately 320 mOsm er liter[17] it was thought that a possible planation for the occurrence of tampo ade was the extraction of serous fluid om the epicardial and pericardial sur ces into the pericardial space This hypo esis was tested in a series of animal experiments designed to evaluate the effect of contrast material injected directly into the pericardial sac

## Materials and methods

Eight adult mongrel dogs weighing from 20 to 25 kilograms were anesthetized with intravenous sodium pentobarbital (25 mg per kilogram) supplemented as required to maintain moderate anesthesia After the insertion of an endotracheal tube respiration was maintained with a Harvard respiratory pump Catheters were positioned in the right and left ventricles via the external jugular vein and carotid artery respectively The chest was opened in the fifth intercostal space and the pericardial sac was cannulated with an open polyethylene tube (I D 1 13 mm ) The polyethylene tube was brought out through the corner of the incision the chest was closed and the lungs were inflated Left and right ventricular pressures and Lead II of the electrocardiogram were monitored continuously on a photographic recorder (Electronics for Medicine) using Statham P23Db strain gauges After control recordings were obtained 65 per cent Hypaque in amounts varying from 0 5 to 1 5 ml per kilogram of body weight warmed to body temperature was injected into the pericardial space through the tubing Heart rate and left and right ventricular pressures were monitored continuously and recorded intermittently over the ensuing period of observation The absence of leakage of dye from the sac was confirmed by frequent fluoroscopy These observations also served as a semiquantitative method of evaluating the volume of fluid in the pericardial space At the termination of each experiment the pericardial fluid was withdrawn and the volume measured In 4 animals the osmolality of both the injectate and the withdrawn pericardial fluid was determined by freezing point depression after serial dilutions with distilled water[18]

Statistical analyses were performed with conventional methods for small samples Differences were evaluated by Student's t test Correlations were measured with the correlation coefficient r

## Results

The effects of the injection of contrast medium into the pericardial sac are summarized in Tables I and II The amount of contrast material injected ranged from 9 to 25 ml with a mean of 16 ml The volume of the pericardial space as seen by fluoroscopy markedly increased in all cases The x ray films in Fig 1 illustrate the size of the pericardial sac immediately after the injection of contrast material and 90 minutes later in Dog No 7 In Dog No 8 the pericardial fluid leaked out into the

*Table I Osmotic effects of the injection of contrast medium into the pericardial sac*

| Dog No | Dose (ml /Kg ) | Time interval for maximum effect (min ) | Volume of dye injected (ml ) | Final volume (ml ) | Initial osmolality (mOsm /L ) | Final osmolality (mOsm /L ) |
|---|---|---|---|---|---|---|
| 1 | 0 5 | 149 | 9 | 55 | 2 866 | 433 |
| 2 | 0 6 | 97 | 10 | 65 | 2 000 | 470 |
| 3 | 0 7 | 109 | 14 | 88 | — | — |
| 4 | 0 8 | 167 | 16 | 10 | 2 670 | 326 |
| 5 | 1 0 | 94 | 18 | 85 | 2 670 | 354 |
| 6 | 1 5 | 117 | 24 | 110 | — | — |
| 7 | 1 5 | 26 | 23 | 107 | — | — |
| 8 | 1 5 | 134 | 25 | Leaked out | — | — |
| Mean values | | 112 ± 42 9 | 16 ± 5 8 | 88 ± 21 4 | 2 551 ± 379 1 | 383 ± 51 5 |
| Significance of differences | | | p < 0 01 | | p < 0 01 | |

*Table II Hemodynamic changes produced by the intrapericardial injection of contrast material*

| Dog No | Heart rate (beats/min ) | Pressures (mm Hg) | | | |
|---|---|---|---|---|---|
| | | *LVSP* | *LVEDP* | *RVSP* | *RVEDP* |
| 1 | 120<br>170† | 130<br>90 | 8<br>7 | 25<br>26 | 6<br>4 |
| 2 | 152<br>160 | 136<br>121 | 3<br>4 | 32<br>24 | 4<br>4 |
| 3 | 160<br>170 | 185<br>121 | 6<br>10 | 30<br>41 | 8<br>8 |
| 4 | 170<br>174 | 196<br>91 | 11<br>21 | 41<br>49 | 7<br>16 |
| 5 | 106<br>96 | 206<br>146 | 9<br>17 | 34<br>33 | 9<br>3 |
| 6 | 186<br>275 | 118<br>109 | 5<br>10 | 30<br>35 | 4<br>10 |
| 7 | 150<br>170 | 87<br>59 | 2<br>5 | 23<br>28 | 2<br>3 |
| 8 | 132<br>170 | 162<br>127 | 7<br>11 | 34<br>24 | 2<br>8 |
| Mean control values | 147 ± 26 | 152 ± 41 | 6 4 ± 3 | 31 ± 5 6 | 5 ± 2 6 |
| Mean final values | 154 ± 40 | 108 ± 7 | 10 6 ± 5 8 | 32 ± 8 9 | ± 4 5 |
| Significance of differences | p < 0 5 | p < 0 01 | p < 0 | p < 0 8 | p < 0 3 |

*Control values
†Final values.
*LVSP* Left ventricular systolic pressure *LVEDP* Left ventricular end-diastolic pressure *RVSP* Right ventricular systolic pressure *RVEDP* Right ventricular end-diastolic pressure



Fig 1 The appearance of the pericardial sac after the injection of contrast material The x ray photograph on the left illustrates the appearance of the pericardial space immediately after injection of 23 ml of contrast material and the x ray film on the right 90 minutes later in Dog No 7

chest cavity after massive expansion of the pericardial sac and therefore the final volume of fluid accumulated could not be measured The amount of pericardial fluid withdrawn at the end of each experiment ranged from 55 to 110 ml with a mean of 86 ml an increase of 550 per cent ($p < 0.01$) For the 4 animals in which measurements were made the average osmolality of the injectate was 2 522 mOsm per liter and of the fluid withdrawn 383 mOsm per liter This indicates significant dilution by solute free water The final osmolality is still somewhat above that found in normal dogs in this laboratory (290 to 300 mOsm per liter) If it is assumed that none of the injectate had left the pericardial sac via capillary and lymphatic drainage the mean final volume in these 4 animals would have been 88 ml Since the mean final volume was 13 per cent less than expected this suggests that a part of the injectate was removed by the vascular or lymphatic systems and that passage across this membrane was bidirectional However in all animals residual pericardial fluid which could not be recovered was present

The time interval necessary for the maximum osmotic and hemodynamic effects to occur ranged from 94 to 167 minutes with the exception of Dog No 7 in which the time was 26 minutes This animal was hypotensive prior to the injection of contrast material (Table II) There was a good correlation ($r = 0.89$ $p < 0.01$) between the volume of contrast material injected and the amount of pericardial fluid withdrawn However it is of interest that there was no correlation between the volume of the injectate and the time required for maximum effect to occur ($r = 0.30$ $p < 0.3$)

The hemodynamic changes produced by the injection of contrast material into the pericardial sac are summarized in Table II Mean heart rate did not change significantly during the experiment ($p < 0.5$) The left ventricular systolic pressure fell (mean fall $44 \pm 11$ mm Hg $p < 0.01$) and left ventricular end diastolic pressure rose (mean rise $= 4 \pm 1$ mm Hg $p < 0.02$) in all but one animal Changes in right ventricular systolic and end diastolic pressures were not significant ($p < 0.8$ and $p < 0.3$ respectively)

Four animals were followed for 3 to 4 hours after the injection of contrast material Left ventricular systolic pressure fell gradually until maximum volume was achieved at a mean time of 105 minutes and then rose gradually thereafter During this period the pericardial sac was seen to expand and then to empty In 3 animals after the maximum hemodynamic effects had occurred and the fluid had been with

drawn and measured the fluid was re injected and an additional amount of normal saline was added to produce cardiac tamponade This required 60 to 85 ml of normal saline and the final fluid volumes were similar to those required in the study of Morgan and associates[11] (100 to 300 ml of normal saline)

## Discussion

Extravasation of contrast material into the myocardium or pericardial sac during selective angiography has been considered to be one of the serious potential complications of this technique[5] Table III shows the incidence of extravasation of contrast material into the myocardium and pericardial space after angiography as reported by several authors[1,2,3,4,5,6,7] In a case reported by Escher and associates thoracotomy was performed for the relief of tamponade It is of interest that an active bleeding site into the pericardial sac was not demonstrated at operation In our patient cardiac tamponade developed after the injection of contrast material into the left ventricle and was treated successfully with pericardiocentesis alone The hematocrit of the pericardial fluid was only 5 per cent indicating the presence of 25 ml of blood (hematocrit of 40 per cent) in the pericardial sac which contained approximately 225 ml of fluid If one estimates that 40 ml of the contrast material extravasated into the pericardial space along with 25 ml of blood and was added to 10 to 15 ml of pericardial fluid that was present initially the final volume estimated is 300 per cent greater than the initial volume In our animal study the mean volume injected was 16 ml and the mean final volume was 88 ml indicating a dilution of 550 per cent by solute free water from the pericardium and the epimyocardial surfaces Therefore it seems to be likely that the cause of the accumulation of fluid and the development of cardiac tamponade after cineangiography in our patient was not active bleeding but the effect of the hypertonic solution Further evidence for this hypothesis is the absence of the recurrence of pericardial tamponade or effusion after removal of the pericardial fluid in our patient as well as in the case reported by Pocock and associates[13]

Although none of the dogs in our experiment developed cardiac tamponade all had significant hemodynamic alterations In 3 animals the addition of 60 to 85 ml of normal saline produced tamponade However these animals had normal hearts and pericardia On the other hand some patients with rheumatic heart disease are known to have extensive pericardial fibrosis and adhesions which may be sufficient to obliterate the entire pericardial space[14] Pericardial disease not only may decrease the distensibility of the pericardium but also may delay the absorption of contrast material from the pericardial space Furthermore cardiac enlargement may reduce the already limited distensibility of a diseased pericardium Finally although in our experiment radiopaque material was injected directly into the

*Table III. The incidence of extravasation of contrast material during cardioangiography*

| *Author* | *Number of cases* | *Myocardial staining* | *Contrast med ext in the pericardial sac without tamponade* | *Cardiac tamponade* |
|---|---|---|---|---|
| Amplatz et al | 280 | | | 1 |
| Bjork et al | 137 | | | |
| | (147 LV punctures) | 3 | 1 | |
| Hilbish and Herdt[6] | 250 | 1 | | 1 |
| Aker et al | 102 | 2 | | |
| Bagger et al | 2958 | 4 | | |
| Lehman et al | 60 | | | |
| | (7 tests) | 7 | 1 | |

pericardial sac the transmyocardial extravasation of contrast material may reduce the ability of the heart to withstand tamponade

Harris and co workers[1] have studied the effect of radiopaque materials injected into isolated closed intestinal loops of dogs They demonstrated a marked augmentation of the volume of fluid in these loops and a decrease in the osmolality of the fluid The same authors showed a decrease in plasma volume after the intragastric injection of contrast medium suggesting that this transudate originated at least in part from the vascular space Lehan and co workers[22] after injecting 4 ml of contrast material into the coronary arteries of dogs observed a massive transfer of myocardial tissue water to the capillaries as demonstrated by a fall of 30 to 50 per cent in coronary sinus hemoglobin hematocrit and serum protein The same authors have shown that the injection of a similar amount of radiopaque material into the iliac vein of the experimental animal produced a fall of only 5 per cent in hematocrit and a fall of 2 per cent in the hemoglobin concentration of the inferior vena caval blood This indicates the importance of the role of the capillary bed in the resultant hemodilution The intravascular injection of contrast material in man has been noted to cause an increase *in plasma volume*[3] *and plasma osmolality*[22,4] It is evident that these agents *because of their hypertonicity exert a* powerful osmotic force on capillaries increasing capillary permeability[1] The capillary wall acts as a semipermeable membrane and allows passage of fluid to neutralize the osmotic gradient exerted by these materials It is our belief that these reports and the results of the present study explain the cause of the accumulation of fluid in the pericardial sac after the extravasation of radiopaque medium

The diagnosis of extravasation of contrast material during cineangiography usually presents no problem because the operator will immediately notice the presence of radiopaque material in the pericardial sac Once the diagnosis is established the patient should be followed closely and therefore if intra arterial and venous catheters are in place they should not be removed The electrocardiogram and arterial and venous pressures should be monitored and the amount of pericardial fluid estimated by intermittent fluoroscopy Since our patient developed cardiac tamponade within 70 minutes and the experimental data indicate that the longest period required to achieve the maximum expansion of the pericardial space was 167 minutes the patient should be followed in the catheterization laboratory for 2 to 3 hours If cardiac tamponade does not occur within this period of time and the patient s condition is otherwise satisfactory the catheters may be withdrawn and the patient returned to his room for close observation If cardiac tamponade supervenes pericardiocentesis should be performed immediately Fluoroscopic guidance is helpful since the pericardial space is well outlined by the contrast material Our patient as well as the patient whose case was reported by Pocock and co workers was treated successfully with pericardiocentesis and the reaccumulation of fluid did not occur Therefore it would appear that this procedure is the method of choice for initial emergency management If the hematocrit of the fluid withdrawn is less than 10 per cent and the patient s condition is stabilized thoracotomy should be delayed because bleeding as the primary cause of tamponade is unlikely

**Summary**

A 58 year old woman with rheumatic heart disease underwent cardiac catheterization Left ventricular cineangiography resulted in the transmyocardial extravasation of contrast material into the pericardial space Cardiac tamponade occurred 70 minutes later One hundred eighteen milliliters of bloody fluid with a hematocrit of 5 per cent was removed by pericardiocentesis and the patient responded without further treatment

In order to explain the mechanism of cardiac tamponade in the absence of significant bleeding 85 per cent Hypaque was injected directly into the pericardial sac of 8 dogs In all animals the left ventricular systolic pressure fell End diastolic pressure rose in 7 of 8 preparations Mean *pericardial fluid contents were augmented*

by 550 per cent This augmentation was directly proportional to the amount of the injectate but unrelated to the time interval necessary for the maximum effect to occur

It is concluded that tamponade which follows the transmyocardial extravasation of contrast material into the pericardial space need not necessarily result from hemorrhage but may be due to the powerful osmotic force placed on capillary walls by this hypertonic solution The initial treatment of these patients by pericardiocentesis is suggested Thoracotomy should be reserved for those patients in whom the withdrawn fluid has a high hematocrit

We are pleased to acknowledge the technical assistance of Mrs Bess Jenkins and Mrs Marguerite T Brown and to thank Miss Christine Berlane for the preparation of the manuscript

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# The electrocardiogram in a case of hemiparalysis of the diaphragm in a newborn infant

*Jerome R Dorkin M D **
*Jerry Ehrlich M D ***
*Camden N J*

Unilateral paralysis of the diaphragm although a rare pediatric problem has been discussed in the literature many times since it was first described by Naumyn in 1902 The last comprehensive report was that of Riley[1] in 1962 When associated with Erb s palsy the prognosis is poorer but the diagnosis is more easily arrived at However Blattner[2] and Schifrin[3] have published cases of isolated hemiparalysis of the diaphragm In these cases the diagnosis is often missed or delayed The present case is published because the diagnosis was suggested on the third day of life by the electrocardiographer before it was suspected clinically In the literature concerning hemiparalysis of the diaphragm available to us there was no mention or description of electrocardiograms The possibility that the electrocardiographic pattern observed in our case may be specific for the condition is therefore worthy of note

### Case report

The mother of the infant whose case is discussed in this report was a gravida iv para iii Negro woman admitted to the Cooper Hospital on March 7 1965 in active labor The prenatal course had been benign except for a slightly excessive gain in weight After 6 hours of labor the membranes ruptured spontaneously The fetal heart rate which had been regular at 140 per minute suddenly began to slow became irregular and then could not be heard Rapid delivery of a 9 pound female infant was effected by a mid forceps extraction over a right mediolateral episiotomy The baby s 1 minute Apgar score was 5 and her cry was delayed for several minutes Because of the low Apgar score fetal distress and cyanosis she was admitted to the premature nursery

On admission to the nursery the infant was cyanotic The respiratory rate was 72 per minute with obvious dilatation of the alae nasi The lungs were poorly aerated and exhibited bilateral crepitations The heart rate was regular at 120 per minute and no murmurs were heard Femoral pulses were equal

Placed in an incubator with 40 per cent oxygen the infant continued to exhibit respiratory distress tachypnea and cyanosis The report by one of us on an electrocardiogram recorded on March 10 1965 (Figs 1 and 2) contained the following statement I wonder if there is not some odd anatomic abnormality perhaps involving the diaphragm which results in extreme movements of the heart in various phases of respiration

The chest x ray film then obtained exhibited some elevation of the right diaphragm (Fig 3) and on March 11 1965 fluoroscopy revealed paradoxical excursions of the diaphragm thus a diagnosis of hemiparalysis of the right diaphragm was established Bronchoscopy was negative

Respiratory difficulty persisted for another 2 weeks with additional x ray films still showing the high right diaphragm Several electrocardiograms continued to show the pattern displayed in Fig 1 but there seemed to be a gradual decrease in the degree of variability of the QRS complexes

By April 6 1965 symptoms of cyanosis and respiratory difficulty had abated and the infant was allowed to go home

Received for publication Nov 12 1965
*Associate Cardiologist and Director of the Heart Station Cooper Hospital Camden N J Address 3908 Federal St Camden 5 N J
**Pediatric Resident Cooper Hospital Camden N J

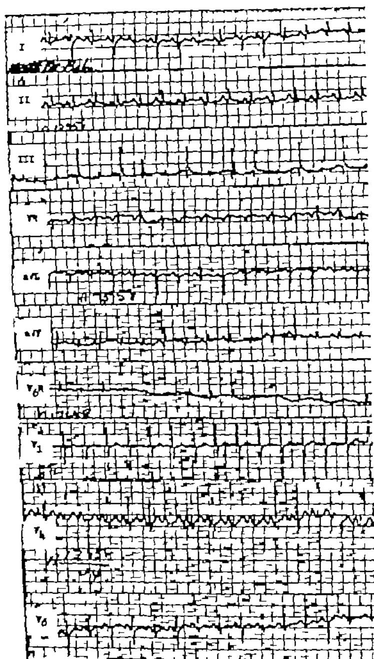



Fig. 1. Initial electrocardiogram recorded on March 10, 1965.

On July 14, 1965, a follow-up chest x-ray film (Fig. 4) showed a normal position of the right diaphragm. The last electrocardiogram (Fig. 5) no longer showed the unusual features noted on the original tracing.

## Discussion

The interesting finding in this case and the reason for this report was the unusual electrocardiogram. At first glance one gets the impression that some of the QRS complexes are premature, but careful measurement indicates a regular rhythm. The P waves occur *regularly* and with no intrinsic variation. The possibility of aberrant ventricular conduction is ruled out by *the fairly constant* QRS duration and




Fig. 2. Enlargement of Leads I, II, and III shows in detail the unusual changes in QRS configuration. *See text.*



Fig. 3. Initial chest x-ray film shows the high right diaphragm.



Fig. 4. Follow-up chest x-ray film recorded on July 14, 1965, shows normal position of the diaphragm.

the lack of any appreciable variation in T. Some QRS complexes consist of a q and a slurred R wave. Others display a qRs, and some are rS complexes. The greatest variability is seen in Leads I and III. If one first calculates the axis using the most negative complexes in Lead I and the most positive complexes in Lead III and then calculates the axis represented by the most positive complexes in Lead I and the most negative in Lead III, one sees that it oscillates between +40 and +134 degrees. The most plausible explanation for this phenomenon could be a swing of the heart about its anteroposterior axis from left to right. It was for this reason that the electrocardiographer suggested such a mechanism, and x-ray examination and fluoroscopy tended to corroborate this impression. The movement of the thoracic contents with respiration was so marked and the mediastinum in the newborn infant was apparently so mobile that the heart was literally swinging about its

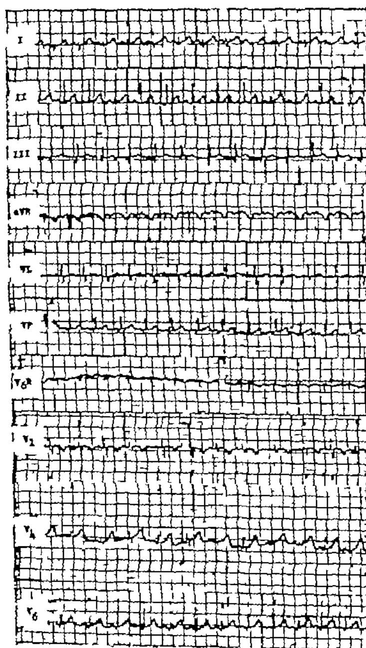



Fig 5 Follow up electrocardiogram recorded on July 14 1963 The tracing is now normal

anteroposterior axis At first thought it seemed to be impossible that the axis could swing from one extreme to the other within one or two cardiac cycles but when one recalls that the respiratory rate was as high as 72 per minute and was typically rapid and jerky the rate of change of the axis is quite believable

A consensus of those observing cases of *hemiparalysis* of the diaphragm indicates that fluoroscopic observation of the see saw movement of the diaphragm is the best diagnostic point This is *Kienbock's* sign and is described in a reference by Light.[4] This seesaw movement of the diaphragm *is the mechanism that causes the* swing of the heart from side to side resulting in the electrocardiographic pattern

seen in our case Our interpretation was further corroborated by the gradual disappearance of the QRS variations as the diaphragm began to respond in a more normal manner At the present time with normal position of the right diaphragm (Fig 4) the electrocardiogram no longer shows any variation of QRS from beat to beat (Fig 5)

A more complete discussion of the clinical and pathologic findings in this disorder is beyond the purview of this report For an excellent review and bibliography the reader is referred to the aforementioned report by Riley[1] Other interesting case reports available to us were those of Tyson and Bowman[4] Blattner[2] Light[5] Turner and Bakst[6] Schifrin[3] Bingham[7] and France[8]

## Summary

An unusual electrocardiographic finding which may be specific for cases of hemiparalysis of the diaphragm in newborn infants is presented

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# Review

## Congenital complete heart block in children

*Charles R. Ayers, M.D.*
*John P. Boineau, M.D.**
*Madison S. Spach, M.D.***
*Durham, N. C.*

Advances in the field of pediatric heart disease have included an improved evaluation of congenital complete heart block. Although associated cardiac malformations must be excluded, there has been increased awareness that this condition probably occurs most frequently as an isolated entity.

Most physicians who care for children with this condition currently believe that those who have no associated heart defects usually do quite well; however, reports in the literature indicate deaths related to this condition. This is a review of the historical aspects of this subject with a presentation of electrophysiologic and hemodynamic factors influencing the findings in this condition. Also, a review of complications which have been reported is presented in an attempt to suggest optimal management for this group of children.

### A. Electrophysiology of heart block

Congenital heart block is the result of a disturbance in the propagation of excitation from the atria to the ventricles due either to an anatomic or purely electrical discontinuity in the specialized conduction pathways which ordinarily connect these two chambers. The studies of Robb and Petri[1] and Paes de Carvalho and associates[2] have demonstrated localized tracts of specialized conduction tissue connecting S-A and A-V nodes. It is not known whether selective ablation of these preferential pathways produces A-V block. The normal appearing QRS configuration in cases of congenital A-V block indicates a relatively normal sequence of ventricular excitation due to a pacemaker located above the bifurcation of His. Wallace[3] has observed that in the dog a pacemaker can be located above the bundle of His after heart block has been surgically produced.

Recent electrophysiologic studies by Hoffman[4] and Paes de Carvalho[5] on the mechanism of atrioventricular impulse transmission indicate that A-V block may result from changes in the electrical characteristics of the cells in the A-V node. These observations are especially significant in view of the possible mechanisms of block in patients with the arrhythmia of congenital advanced but not complete A-V block.

In the presence of a physically intact conduction pathway between atrium and ventricle, advanced degrees of A-V block are attributed to prolongation of the recovery period of excitable cardiac tissue

From the Department of Pediatrics, Duke University Medical Center, Durham, N. C.
This work was supported in part by United States Public Health Service Grants HE-1549 and HTS-5372.
Received for publication Dec. 29, 1963.
*Special Postdoctoral Fellow, National Heart Institute, United States Public Health Service.
**Address: Division of Pediatric Cardiology, Duke University Medical Center, Durham, N. C. 27706.

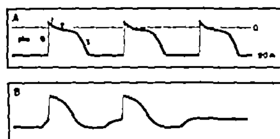



Fig. 1. Transmembrane action potentials of ventricular and A-V nodal fibers. A, The refractory period of ventricular myocardium. The five phases (0 through 4) of an action potential of a ventricular fiber are illustrated to demonstrate the relationship between the recovery of excitability and the refractory period. From the beginning of excitation (Phase 0) through Phase 2 the fiber is refractory to the arrival of a premature impulse. Impulses occurring during the latter part of Phase 3 and during Phase 4 normally result in excitation of the fiber. *B*, Refractoriness of A-V nodal tissue due to decremental conduction. The principle of refractoriness of specialized A-V node fibers to impulse propagation involves decremental conduction. The consecutive beats shown illustrate the characteristic initial slow rise ("foot") of nodal fibers of the N region of the A-V node. Note the progressive lengthening of the initial "foot" (decremental conduction) with failure to reach the necessary threshold for impulse propagation in the third beat.

Fig. 1*A* diagrammatically illustrates the four phases of an action potential from a ventricular fiber of the dog. A natural impulse arriving between Phase 0 and Phase 3 is not likely to excite cells at this stage of recovery and therefore will not be transmitted to more distal tissues. The absolute refractory period of excitable tissue corresponds to Phase 2 and part of Phase 3. The latter part of Phase 3 corresponds to the relative refractory period: excitation and propagation are more likely to occur when a stimulus is received at this stage. Phase 4 corresponds to the resting potential of the polarized cell, and the tissue is readily depolarized during this period.

Although the relative and absolute refractoriness of myocardial tissue is meaningful in terms of a naturally generated impulse, the distinction is somewhat arbitrary under experimental conditions. Excitation has been found to depend on the strength and duration of an applied stimulus during the various phases.[4]

The term *refractoriness* as applied to the mechanism of delayed or blocked impulse transmission through the A-V node region is of a different order. Paes de Carvalho[5] has demonstrated different electrical properties of cells located in three regions of the A-V node—the atrionodal (AN), nodal (N), and nodal-His (NH) regions. He as well as Hoffman[4] have noted that both normal and abnormal delay or block in impulse transmission is localized to the N region. They have demonstrated that progressive delay with characteristic Wenckebach cycles can be produced with repetitive premature stimulation, acetylcholine, and anoxia. The transmembrane potential curve of these cells has a distinctive initial slow rise ("foot") from which the action potential occurs. With rapid atrial stimulation or exposure to acetylcholine, delay in excitation occurs with progressive lengthening of the "foot." Failure of propagation results when the initial rise fails to reach a critical threshold (Fig. 1 *B*).

It is probable that a critical density of current is necessary for impulse propagation. If transmission is progressively slow or decremental, this threshold is not attained. This mechanism is referred to as *decremental conduction*[4] and can be used to explain advanced and possibly complete A-V block if an insufficient number of cells are simultaneously excited because of partial interruption of the pathway.

Atrioventricular dissociation is a useful electrocardiographic term to describe independent control of atrial and ventricular excitation by separate pacemakers. Three mechanisms of A-V dissociation that may operate singly or in combination in a given patient are the following: (1) Complete or incomplete physical discontinuity in the pathways of A-V conduction resulting in complete A-V dissociation due to complete forward block (e.g., congenital complete heart block with absence of the A-V node). (2) Electrical discontinuity due to abnormal properties of cells of the N region of the A-V node resulting in A-V dissociation and second degree, advanced, and possibly even complete A-V block due to varying degrees of decremental concealed conduction (e.g., second degree heart block with Wenckebach cycles). (3) Normal interference of impulse transmission due to (*a*) the collision of excitation waves from two

pacemaker sites one located above and the other in or below the A V node prior to the His bifurcation (b) normal block in the A V node producing failure to transmit some of the impulses arriving from rapid repetitive stimuli with the expected decrement in the N region and (c) concealed A V conduction with peripheral block because of failure to excite Purkinje or myocardial tissue due to the arrival of the impulse during an absolute refractory period of these tissues

Atrioventricular block in patients with rapid atrial rates as occurs in atrial flutter with a 2 1 block is an example of mechanism 3b Atrioventricular dissociation in which the sinus pacemaker occasionally captures the ventricle principally involves mechanisms 3a and c However for the dissociation to persist retrograde block (mechanism 2 in reverse) must be implicated to explain the absence of atrial capture by the ventricle when the rate of the atria is slower than that of the ventricles Similarly some degree of forward block must be present in A V dissociation when the rate of the atrium is faster than that of the ventricle and only infrequent ventricular captures by atrial pacemaker are observed Because of this fundamental relationship between A V block and A V dissociation a dynamic approach is essential in the evaluation of an individual clinical arrhythmia The electrocardiogram in Fig 2 *B* illustrates a case of presumed congenital advanced A V block The basic mechanism appears to be second-degree A V block with a typical Wenckebach period involving $P_1$ $P$ and $P_3$ ($P_3$ is blocked) However $P_4$ should have been conducted

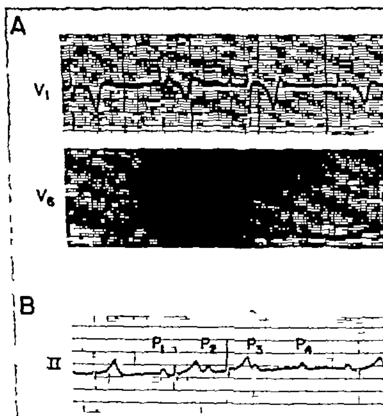



Fig 2 Typical and atypical electrocardiograms in children with heart block *A* Complete atrioventricular dissociation due to complete A V block Note that there is no relationship between the P waves and QRS complexes which are of normal duration *B* Complex arrhythmia demonstrating advanced A V block in a 7 year-old child The mechanism of this arrhythmia is discussed in the text

lost consciousness and became moribund Immediate application of an external pacemaker at a stimulation rate of 120 per minute produced a dramatic change Within 1 minute the child regained consciousness and with continued pacing he became quite alert and showed marked diminution in respiratory rate after 5 minutes While pacing was continued cardiac catheterization was promptly carried out with documentation of a patent ductus which was surgically corrected Thereafter the child became asymptomatic

Review of the literature suggests that the prognosis in congenital heart block is related primarily to cardiac adaptation to stress and to the occurrence of Stokes Adams attacks (which may be caused either by ventricular asystole or ventricular tachycardia and fibrillation) The newborn period presents an especially vulnerable time for these patients Reports of mortality occurring in the newborn period suggest[22 23] that such infants with heart rates of less than 50 beats per minute are especially likely to succumb Later in infancy the occurrence of febrile illnesses may also produce a hazardous situation[7 24] The mechanisms of poor adaptation of the newborn and infant to stressful situations remains to be clarified however superimposed metabolic acidosis leading to further slowing of heart rate may be an important factor In these situations intermittent external pacemaker therapy may *be lifesaving*

Elucidation of the incidence of Stokes Adams attacks in children with congenital complete heart block is difficult although such episodes are considered to be infrequent However evidence is strong that patients with congenital complete heart block with a widened QRS complex (idioventricular pacemaker ?) are especially prone to such episodes[7 21 1] In these patients with broad QRS complexes one is faced with the question of whether permanent pacemaker implantation is indicated The high incidence of death in this particular group suggests strong consideration of this method of therapy if Stokes Adams episodes develop Also in any child with complete heart block who has had two or more Stokes Adams attacks permanent pacemaker therapy should be strongly considered as suggested by Nakamura and Nadas[1]

Molthan and associates[21] reported on thirty five children with congenital complete heart block and of these three died with Stokes Adams attacks (all of these had electrocardiographic evidence of a widened QRS complex) Nakamura and Nadas reported on sixty one children of whom thirty had associated congenital cardiac defects suspected clinically or documented at catheterization In their series one death occurred in a child shown to have no cardiac defects and an additional twelve who had associated heart disease died during childhood The mechanism of death in their patients was primarily sudden onset of severe congestive heart failure

In our own experience we have followed twenty children with congenital complete heart block in the past 6 years Of these five have had evidence suggestive of associated heart disease and have undergone cardiac catheterization Of those catheterized two had no associated defects one had a secundum atrial septal defect and two had patent ductus arteriosus Those with congenital defects underwent surgical correction Two years postoperatively the child with the secundum atrial defect whose QRS was of normal duration died suddenly at home By history the episode was a characteristic Stokes Adams attack Thus one patient of the total group of twenty *developed Stokes Adams syndrome* and died

The question remains as to the optimal management of the asymptomatic child with congenital complete heart block who has no evidence of associated congenital heart disease Although periodic checkups are indicated these patients should be managed as normally as possible The physician caring for this group of children is in a dilemma when asked what the ultimate fate of such children will be in adult life This important information can only be available after large series of children with congenital heart block have been followed into adult life

## Summary

Although absolute evidence of the congenital nature of the heart block rests upon

the diagnosis being made before or immediately after birth, children shown to have complete heart block at a later age who have a QRS complex of normal duration and who have a negative history for inflammatory diseases which might cause heart block should be considered and managed as though they had congenital complete heart block. The prognosis in this condition is largely related to cardiac adaptation to stress and to the occurrence of Stokes-Adams attacks. Increased stress leading to severe congestive heart failure is most likely to occur during the newborn period and during febrile illnesses in infancy. Also associated cardiac malformations place the patient in a vulnerable position with the possibility of the onset of rapid heart failure. Stokes-Adams attacks are most likely to occur in those children who have widened QRS complexes electrocardiographically. Although it is difficult to clarify the true instance of Stokes-Adams attacks in children who have complete heart block with a supraventricular pacemaker, such episodes are unusual. During episodes of increased stress in which heart failure is likely to occur, intermittent external pacemaker therapy may prove to be lifesaving. The difficult problem of therapy for repeated Stokes-Adams attacks should be approached with consideration of permanent pacemaker therapy.

Those patients without symptoms and/or associated heart disease generally do well and should be managed as normally as possible with intermittent checkups. In view of the absence of reports concerning the ultimate fate of a large series of children with documented congenital heart block, valuable information would be provided by a long-term cooperative investigation between cardiology groups caring for children and adults to elucidate the course of such children as they proceed into adult life.

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## The clinical significance of true left axis deviation

### Left intraventricular blocks


*Ray Pryor, M.D.**
*S. Gilbert Blount, Jr., M.D.***
*Denver, Colo.*


With rare exception, true left axis deviation is an abnormal electrocardiographic finding. This communication will deal with the pathophysiology, causes, and clinical significance of left axis deviation in acquired and congenital heart disease. Left inferior intraventricular blocks will be briefly compared with left superior intraventricular blocks.

#### Definition of terms

*True left axis deviation* (*LAD*)—Deviation of the mean QRS axis (ÂQRS) to the left and superior of 330 degrees (−30 degrees), i.e., between 270 (−90) and 330 degrees in the frontal plane (Fig. 1).

*Mean QRS vector* (*ÂQRS*)—The average of all instantaneous vectors during the QRS interval.

*Initial QRS vector*—The average of all instantaneous vectors during the first 0.04 second of the QRS interval.

*Terminal QRS vector*—The average of all instantaneous vectors during the last 0.04 second of the QRS interval.

#### Anatomy of left ventricular conduction system

A brief review of the conduction system of the left ventricle is pertinent and will make the discussion of peripheral left intraventricular conduction defects more logical.

At the tip of the interventricular septum the common bundle bifurcates into a right and left bundle branch. Shortly after the left bundle appears on the left side of the interventricular septum, it divides into two groups of fibers. One group fans out as a radiation of fibers that spreads superiorly and anteriorly over the subendocardium of the anterolateral wall; this group is called the superior (anterior) division of the left bundle. The second group also fans out but radiates inferiorly and posteriorly toward the inferior surface of the left ventricle; it is called the inferior (posterior) division of the left bundle. Fig. 2 illustrates these divisions or radiations viewed through the left ventricle. Many investigators[1-13] have observed these two major divisions of the left bundle, whereas others[14] reported that the left bundle appeared to fan out over the endocardial surface of the left ventricle but discrete separate divisions were not described. It is important to at least conceptualize the fibers of the left bundle as being arranged into superior and inferior divisions in order to rationally approach


From the Division of Cardiology, Department of Medicine, University of Colorado Medical Center, Denver, Colo.


Received for publication May 23, 1966.


*Assistant Professor of Medicine, Division of Cardiology. Address: University of Colorado Medical Center, [illegible] E. Ninth Ave., Denver, Colo. [illegible]
**Professor of Medicine, Head, Division of Cardiology.

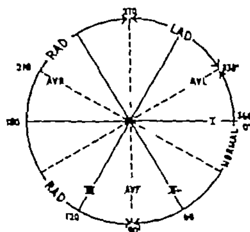



Fig 1 The frontal plane reference figure demonstrating the boundaries of LAD RAD and normal AQRS

the diseases that alter the sequence of depolarization of the myocardium supplied by these radiations These two divisions of the left bundle freely anastomose peripherally in the subendocardial layers of the ventricle via a network of Purkinje fibers

### Electropathophysiology of left intraventricular blocks, including peri infarction blocks

Normally excitation spreads simultaneously along both divisions of the left bundle If a lesion should involve a sufficiently large number of fibers of one division the sequence of excitation would be altered If the lesion should dominantly involve the superior division fibers excitation would spread down the inferior fibers travel through Purkinje anastomoses and finally spread superiorly the QRS loop would be counterclockwise the terminal QRS vector would point leftward and superiorly and LAD would occur As long as the conduction system was used throughout excitation there would be little or no QRS prolongation but if the lesion was extensive or so situated as to force excitation out into the slowly conducting myocardium QRS prolongation would occur because of a broad terminal vector (slowing of the terminal forces of the loop) If the lesion involving the superior division is *fibrosis* the initial QRS vector will be inferior and leftward (normal) the terminal vector superior and leftward and LAD will be the result (Fig 3 A) This type of conduction defect may be called *left superior intraventricular block* (SIVB) or parietal block of the superior division of the left bundle the former being preferable If the lesion is *necrosis* (infarction) the direction of the terminal vector and AQRS will be similar to that for the previous conduction defect but the initial vector will be directed

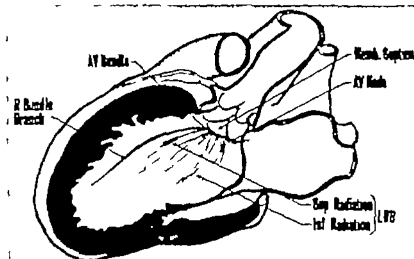



Fig 2 Drawing of the superior and inferior radiations of the left bundle viewed through the left ventricle (Courtesy of Dr Robert I Hawley Denver Colorado )

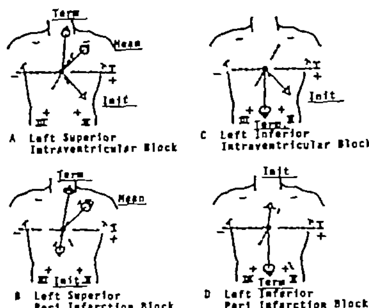



Fig 3 A Drawing of the vectors for superior intraventricular block (SIVB) B Superior peri infarction block (SPIB) C Inferior intraventricular block (IIVB) D Inferior peri infarction block (IPIB)

inferiorly and rightward (abnormal) away from the infarcted area in the superior or anterior lateral wall (Fig 3 B) This type of conduction defect may be called *left superior peri infarction block* (SPIB) or *postinfarction block* The word superior is used instead of anterolateral in order to maintain continuity of terminology with the anatomy of the conduction system and with the other location of intraventricular blocks

Experimental work with laboratory animals supports the concept that lesions involving the superior division may cause the terminal QRS forces to shift leftward and superiorly In separate experimental studies Uhley and Rivkin[14] and Watt and Pruitt[15] observed this leftward and superior rotation of QRS forces after laceration of the superior (anterior) radiation of the left bundle in dogs In another study Watt Murao and Pruitt[17] found an even greater leftward and superior shift of the mean electrical axis in the frontal plane (sufficient to satisfy criteria for clinically significant left axis deviation in human beings) after laceration of the anterior rami of the left bundle branch in the baboon (primate) heart as compared to the canine heart study [16]

Although the remainder of this paper will deal with causes and clinical significance of LAD at this point it is appropriate to briefly discuss and illustrate the counterpart of superior intraventricular blocks namely left inferior intraventricular blocks

Should there be a necrotic lesion in the inferior wall involving the fibers of the inferior division of the left bundle the initial QRS vector would point leftward and superiorly away from the inferior infarct Excitation of the inferior wall would occur from above the QRS loop would be clockwise and the terminal vector would point inferiorly (90 degrees) This type of intraventricular conduction defect may be termed *left inferior peri infarction block* (IPIB) or *postinfarction block* (Fig 3 D) Inferior peri infarction block is illustrated in Fig 4 but will not be discussed further in this paper

LAD due to superior peri infarction block (necrosis) or superior intraventricular block (fibrosis) [4 5 6 7] and inferior peri infarction block (necrosis)[2 3 ... 22 23 24] are well described and largely accepted as electrocardiographic entities Why not *left inferior intraventricular block* (IIVB) or parietal block of the inferior division

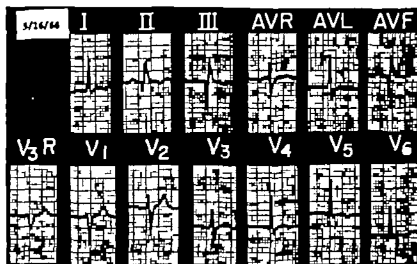



Fig 4 Fifty-one year-old man with ECG illustrating inferior infarction and inferior peri infarction block (IPIB)

of the left bundle due to fibrosis only without necrosis? This entity was recently suggested[19] but has otherwise been undescribed probably because the electrocardiogram would appear to be normal We believe that inferior intraventricular block may be a recognizable electrocardiographic entity and will herewith be described and compared with superior intraventricular block

If fibrosis in the left ventricle involves predominantly the distribution of the inferior division of the left bundle the sequence of excitation may be altered in a fashion opposite to that of SIVB Excitation would spread initially through the superior division and then travel inferiorly giving a clockwise loop and a rather inferior (90 degree) terminal QRS vector (Fig 3 C) In both superior and inferior intraventricular block the initial 0 04 second vector is directed inferiorly and leftward (normal) However the very early QRS forces e g the 0 02 second vector direction may be slightly different when the two types of block are compared In SIVB excitation starts down the inferior division thus the 0 02 second vector may be more inferior accounting for the small 0 02 second r wave in Leads II III and aVF and the small 0 02 second q wave in Lead aVL Conversely in IIVB initiation of excitation through the superior division usually causes the 0 02 second vector to be oriented a bit more superiorly causing a small initial 0 02 second r wave in Lead aVL and small 0 02 second q waves in Leads II III and aVF The terminal QRS vector points toward the blocked (by fibrosis) radiation in each type of intraventricular block SIVB is easily recognized by the finding of LAD (abnormal) with a normal initial 0 04 second vector

How may we postulate that IIVB be recognized? It is apparent that the previously described initial vector terminal vector and QRS loop in IIVB outlines a normal electrocardiogram—but normal for whom? As people get older the terminal QRS vector tends to become directed more and more horizontally leftward but not superiorly enough to cause LAD On the basis of the foregoing discussion it is logical to predict that IIVB will be manifested by an unusually inferior terminal QRS vector in a patient who should not have this direction of terminal forces i e a patient more than 45 years old with a medium to heavy body build especially if left ventricular enlargement is coexistent An inferior terminal QRS vector is normal in young people and in older people who are tall or slender Right ventricular enlargement must be clinically excluded as the potential cause of the inferior terminal vector The initial and terminal vectors for IIVB due to only fibrosis are depicted

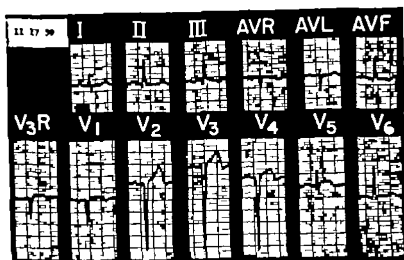



Fig. 5 Fifty five year-old man. ECG shows anterolateral infarction, left ventricular enlargement (LVE), and an unusually inferior terminal QRS vector for age and LVE; thus possible inferior intraventricular block (IIVB) is suggested. *Autopsy* revealed anterior infarction, no inferior infarction, left ventricular enlargement, and no right ventricular enlargement. Fibrosis involving the inferior division of the left bundle was found on histologic study. (Courtesy of Dr. Robert L. Hawley, Denver, Colorado.)

in Fig. 3 C. Experimental work suggests that IIVB should be real rather than hypothetical. Uhley and Rivkin[1] and Watt and Pruitt[14] found that the terminal QRS forces shifted inferiorly after laceration of fibers of the inferior division of the left bundle. We have collected many clinical cases of IIVB and in the majority of these the patients were found to have ischemic heart disease, hypertension, or diabetes, and many had left ventricular enlargement. We have found only 2 cases of IIVB that have come to autopsy and had careful histologic examination of the proper areas of the myocardium for lesions. The electrocardiogram in Fig. 5 was taken on a 55 year old patient with a medium body build and clinical ischemic heart disease. Recent anterior infarction and left ventricular enlargement are apparent. The terminal QRS vector is unusually inferiorly directed for age, body build, and left ventricular enlargement. Clinically, right ventricular enlargement was not present. Thus this electrocardiogram was believed to be suggestive of IIVB (parietal block of the inferior division of the left bundle). The initial QRS vector is somewhat superior but the q waves in Leads II and aVF are not broad enough to be read as indicating inferior infarction. Admittedly, the frontal plane vectors could be due to old inferior infarction with inferior peri-infarction block and partial normalization (narrowing of previously 0.04 second Q waves) of the initial vector. Gross postmortem examination revealed left ventricular enlargement, no right ventricular enlargement, recent anterior infarction, and no inferior infarction. Careful histologic examination showed significant fibrosis involving the inferior division of the left bundle.[32] The other autopsied case of clinical IIVB also revealed fibrosis involving the inferior division. More work needs to be done in this area, especially with carefully planned clinical pathologic correlative studies.

## Causes and clinical significance of left axis deviation

*Superior intraventricular block* (*SIVB*). Reports stating the incidence (0.2 to 1.2 per cent) of LAD found in electrocardiograms taken on healthy, asymptomatic adults[33-36] and the occurrence (0 to 1.4 per cent) of LAD in normal children[34,35] confirm the view that LAD is rarely a normal electrocardiographic finding. Hiss, Lamb, and Allen[36] showed only a 0.8 per cent incidence of *true* LAD in their study of 67,375 asymptomatic sub-

jects and most of the patients with LAD were more than 40 years old

It has been shown that LAD is not related to the position of the heart in the chest or to body build[17] Aging alone is not a significant factor in LAD[18]

Originally LAD tracings without peri-infarction block were called parietal block tracings but later Grant[4] suggested that parietal and peri-infarction block were members of a family of ventricular conduction defects which as a group should be called left intraventricular blocks We like this term but have added the word superior to fit the anatomy and to separate SIVB from the previously postulated IIVB

The most common cause of LAD is *SIVB due to fibrosis caused by ischemic heart disease* Several clinical and electrocardiographic pathologic correlative studies[2,3,12,13,20] show a high degree of corre

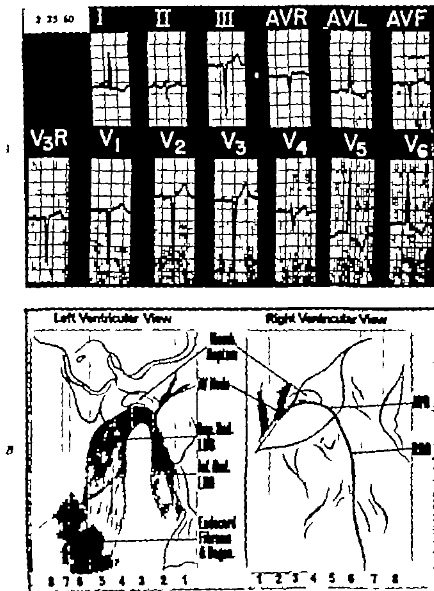



Fig 6 A ECG from a 55 year-old man illustrates LVE LAD and superior intraventricular block (SIVB) *Autopsy* revealed LVE B During histologic study a fibrotic lesion involving the superior radiation of the left bundle was found (Courtesy of Dr Robert I Hawley Denver Colorado )

lation between LAD and clinical cardiovascular disease or left ventricular lesions (fibrosis necrosis or myocardiopathy) In our own study [30] we collected 302 new cases of LAD over a 5 year period Clinical correlation revealed that more than 80 per cent of the patients had ischemic heart disease hypertensive cardiovascular disease diabetes obesity or aortic valve disease SIVB was the reading in 84 per cent of the electrocardiograms Twenty eight of the patients with SIVB came to postmortem examination and 27 had coronary artery disease Twenty four of these 27 patients were found to have fibrosis only whereas the other 3 had old myocardial infarctions Two of these 3 patients with infarction showed old antero lateral infarction on the electrocardiogram without fulfilling the criteria for superior peri infarction block (SPIB) No abnormality of the heart was described in 1 autopsied patient with LAD In a separate double blind electrocardiographic pathologic correlative study [31] all of 8 autopsied patients with LAD were found to have lesions of the superior radiation with SIVB correlating with fibrosis and SPIB correlating with necrosis each time The electrocardiogram (ECG) shown in Fig 6 *A* was taken on one of the patients in this study Left atrial enlargement (LAE) and left ventricular enlargement (LVE) with ST T changes are seen The

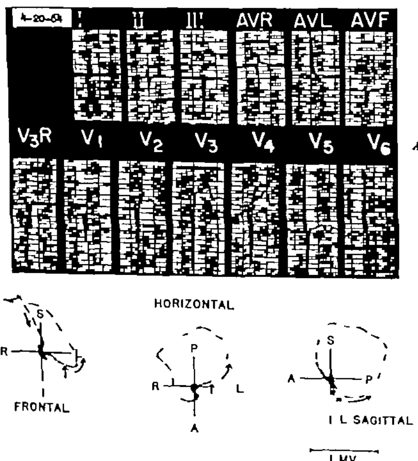



Fig 7 Fifty year-old man *A* ECG demonstrates LVE LAD SIVB and old anterior infarct on *B* VCG (Frank lead system) confirms the anterior infarct since the 0 0 -second vector is posterior to the 0-180-deg (R L) line in the horizontal plane Note normal initial forces counterclockwise loop superior terminal forces and LAD in the frontal plane

initial QRS vector is leftward and inferior (normal), the terminal vector is leftward and superior, resulting in LAD due to SIVB. Postmortem examination revealed coronary artery disease and a fibrotic lesion involving the superior radiation was found by the pathologist during serial histologic studies of the conduction system. The lesion is depicted in Fig. 6 *B*.

The ECG in Fig. 7 *A* shows LVE and LAD due to SIVB. But is the poor r wave progression in Leads $V_3$ to $V_4$ due only to LVE or is there an associated old anterior infarct? The vectorcardiogram (VCG) has proved to be very helpful in the recognition of anterior infarction in patients with LVE.[20] In the *horizontal plane* the 0.02 second vector is anterior to the 0-180 degree line with LVE alone but is posterior to that line with anterior infarction. The VCG in Fig. 7 *B* is compatible with anterior infarction. Of course, the ECG could represent SPIB with normalized initial forces in the frontal plane, but since the criteria for SPIB are not met, the ECG is read as indicating LVE, LAD, SIVB, old anterior infarction, and ischemia.

LAD may be present in patients with marked LVE, especially when due to aortic incompetence; however, the LAD is not due to the LVE alone but suggests fibrosis in addition.

Left bundle branch block (LBBB) is an *interventricular* conduction defect manifested by a leftward shift of the very early QRS forces from a control ECG, QRS broadening, secondary ST-T changes, a narrow QRS loop, and a normal leftward axis in the frontal plane. If an ECG with LBBB shows LAD, additional superior *intraventricular* block is suggested. The ECG shown in Fig. 8 *A* illustrates LBBB, LAD, and SIVB. The tracing in Fig. 8 *B* was taken on the same patient 2 years and 7 months later when the LBBB was not present. The early initial forces have shifted rightward (new small q in Lead aVL and r in Lead III), which proves that the previous ECG indicated LBBB. LAD is still present, suggesting that LAD with LBBB does mean SIVB also. The ECG with LBBB and LAD in Fig. 8 *C* was taken on a patient who died with sarcoid heart disease. Postmortem examination revealed extensive lesions involving both the proximal main left bundle and the peripheral superior division, thus providing pathologic correlation with the LBBB and the LAD.[11]

Right bundle branch block (RBBB) is an interventricular conduction defect characterized by QRS broadening and a broad slurred terminal blocked right bundle vector that is directed rightward and anteriorly, causing the broad terminal S in Lead I and R in Lead $V_1$. With RBBB the sequence of left ventricular excitation is not altered; therefore, the unblocked (before the RBBB comes in) initial, mean, and terminal vectors should be normal. If there is LAD of the unblocked mean (first 0.06 to 0.08 second of QRS interval) vector, it carries the same connotation as LAD without RBBB. The ECG in Fig. 9 *A* shows LAD due to SIVB. The ECG in Fig. 9 *B* was taken on the same patient 9 years later. RBBB has occurred, but the unblocked QRS forces still show LAD; thus SIVB can be read in the presence of RBBB.

LAD has been reported in diseases that involve the myocardium primarily or secondarily, e.g., LAD was found in 64 per cent of patients with *obscure cardiomyopathy*,[14] in 50 per cent of subjects with *cryptogenic cardiomyopathy*,[19] in 19 of 35 patients with *idiopathic myocardial hypertrophy*,[44] and in 7 of 9 patients with *scleroderma*.[4] Sixteen of our 51 patients with *cardiac amyloidosis* had LAD.[41] LAD has also been reported in *myotonia atrophica*, *progressive muscular dystrophy*, *Friedreich's ataxia*, *myocarditis*, *familial cardiomyopathy*, *hemochromatosis*, and *alcoholic cardiomyopathy*.[36]

The type of ECG changes, if any, caused by fibrosis, amyloid, etc., may depend on the relative degree of involvement of certain areas of the myocardium and on the amount of coverage given to these areas by the superior and inferior divisions of the left bundle. In some hearts histologic study reveals that the superior radiation is more dominant in distribution. If the lesion predominantly involved the area of the fibers of the superior division, SIVB might occur. If involvement of the inferior division predominated, inferior intraventricular block might be seen on the ECG. If the disease process in the

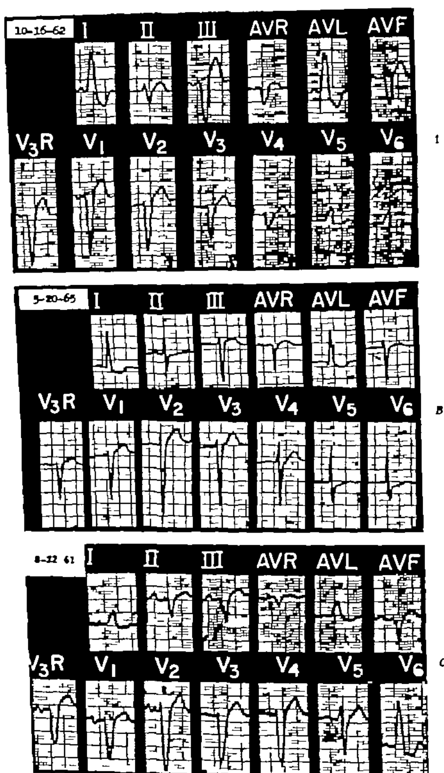



Fig. 3. A, Sixty-three-year-old woman whose ECG shows left bundle branch block (LBBB) and LAD suggesting SIVB. ECG taken 2½ years later (B) does not show LBBB but LAD and SIVB persist. C, ECG from a 35-year-old man with sarcoid heart disease illustrates LBBB, LAD, and SIVB. Autopsy revealed sarcoid lesions involving both the main left bundle and the fibers of the superior division.

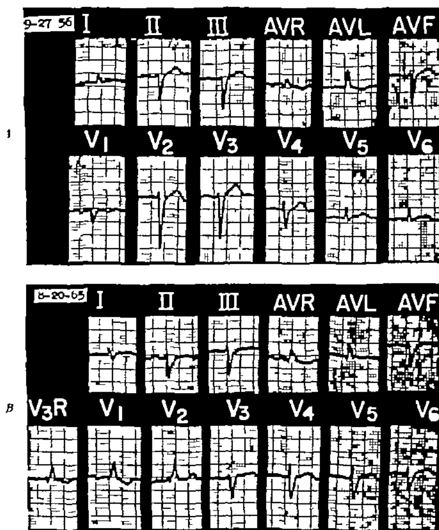



Fig. 9. Forty-six year-old man. *A*, ECG demonstrates LAD and SIVB. *B*, ECG 9 years later reveals right bundle branch block (RBBB) but LAD of the unblocked QRS forces and SIVB can still be read in the presence of RBBB.

myocardium was diffuse and widespread, some degree of electrical neutralization of forces might cause the terminal vectors to be directed normally and thus there would be no recognizable intraventricular block. Occasionally, extensive diffuse involvement of the heart with amyloid has caused the initial and terminal forces to point away from the left ventricle, i.e., at 210 degrees.

*Hyperkalemia* is a potential cause of LAD that has not been previously reported. We have seen several patients who had hyperkalemia and LAD that disappeared after dialysis and a return of the serum potassium to normal levels. The ECG in Fig. 10 *A* was taken when the patient's serum potassium was 8.0 mEq. per liter. The tall T waves and QRS broadening (the initial and terminal forces participate in the widening) of hyperkalemia are apparent and LAD is present. After dialysis, when the serum potassium was normal, the ECG in Fig. 10 *B* was recorded and is observed to be normal without LAD. The pathogenesis of LAD with hyperkalemia is not known at this time. The answer will probably be found in myocardial cellular metabolism.

*Surgical injury* of the superior division of the left bundle is a cause of LAD. Transient LAD occurred in one of our patients

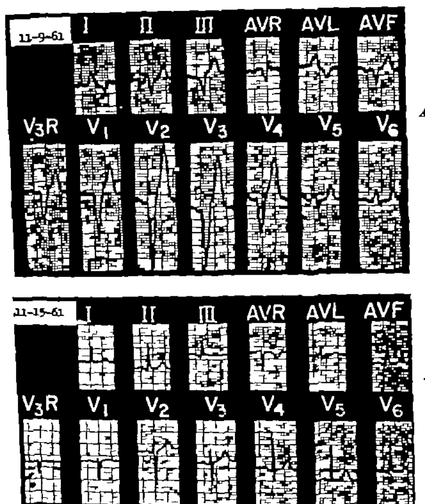



Fig. 10. *A*. Fifty-eight year-old woman with hyperkalemia (serum potassium = 8 mEq./L.). ECG is compatible *with hyperkalemia and LAD noted. B. After dialysis the serum potassium and the ECG returned to normal.*

immediately after mitral valvulotomy with a transventricular dilator. LAD has been reported to occur after transventricular aortic commissurotomy.[4] After surgery for both congenital discrete fibrous subaortic stenosis and idiopathic hypertrophic muscular subaortic stenosis (IHSS) several of our patients have developed LAD with a marked leftward and superior shift of the terminal QRS vector. This suggests that a proximal lesion or damage to the superior division early in its course in the interventricular septum is capable of causing LAD and SIVB. The ECG in Fig. 11,*A* is a preoperative control tracing from a patient with IHSS demonstrating LAE, LVE, and ST-T changes. At operation a relatively large amount of hypertrophic left septal muscular tissue was removed. Immediately after operation the ECG showed LBBB and LAD (Fig. 11,*B*) suggesting surgical damage to both the left bundle and to its superior division. Seven months after operation (Fig. 11,*C*) the LBBB had disappeared but the LAD was still present compatible with permanent surgically induced SIVB. The development of LAD after operation for the abovementioned two types of subaortic stenosis in 4 different patients is comparable with the experimental animal studies quoted earlier.[11]

*Pulmonary emphysema* has been said to be a cause of LAD. Most patients with parenchymal lung disease and varying degrees of right ventricular enlargement

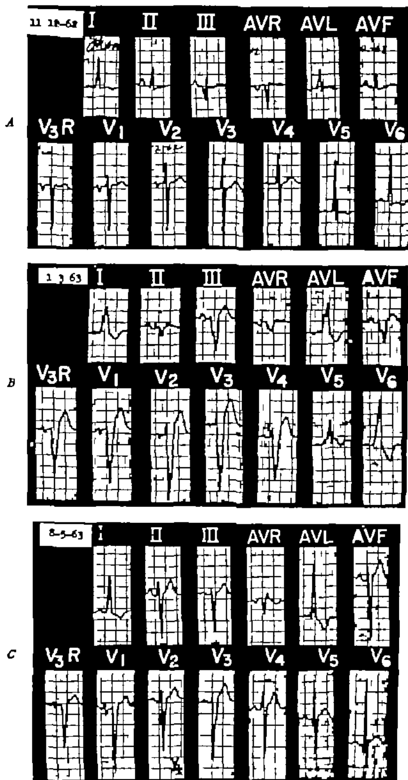
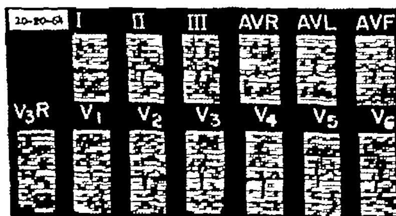



Fig. 11. *A*, Twenty-three-year-old man with idiopathic hypertrophic subaortic stenosis (IHSS). ECG shows left atrial enlargement (LAE) and LVH. *B*, After removal of a moderate amount of hypertrophic left septal tissue, LBBB and LAD developed because of surgical injury of the left bundle and its superior division. *C*, Seven months after operation the LBBB had disappeared but persistent LAD suggests permanent damage to the superior division.

(RVE) will show in the frontal plane a rightward terminal QRS vector with right axis deviation and a clockwise loop or $S_1S_2S_3$ pattern (normal leftward inferior initial vector, rightward superior terminal QRS vector, and an unplottable ÂQRS because of rotation of the loop through the electrical center of the heart in traveling toward the right shoulder terminally). In patients with emphysema the terminal QRS vector may be rightward and superior in the frontal plane, but not uncommonly the loop rotates counterclockwise, causing the ECG to resemble that of LAD. For this type of ECG of emphysema we prefer the term *pseudo LAD* since the ECG of emphysema is usually easily recognized and thus distinguished from that of left ventricular conduction defects. Grant[4] suggested that the abnormal conductance of the emphysematous lungs deforms the electrical field surrounding the heart, which might explain the unusual loops in some of these patients. The pseudo-LAD of emphysema (usually due to RVE) may be distinguished from the true LAD of left SIVB by the following characteristics. The P vector is relatively inferior, causing an inverted P wave in Lead aVL, a flat P in Lead I, and prominent P waves in Leads II, III, and aVF. The QRS voltage is usually low in the limb and precordial leads. The terminal QRS vector is very superior but usually somewhat rightward, causing a small terminal s wave in Lead I and a terminal R wave in Lead aVR that equals or exceeds the terminal R wave in Lead aVL.



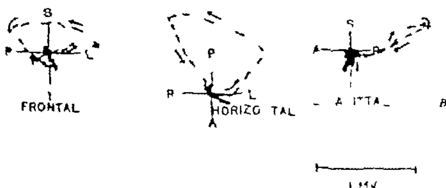




Fig. 1. *A*, Fifty-eight year-old man with emphysema. Note the inferior P vector, low QRS voltage, and superior rightward terminal QRS vector with counterclockwise loop. Lead aVR resembles Lead aVL. ECG illustrates the *pseudo-LAD* of emphysema. *B*, Frank lead system VCG shows the superior rightward terminal QRS vector with counterclockwise loop in the frontal plane—probably representing right ventricular enlargement with the electrical field influenced by the emphysematous lungs.

The P wave, QRS, and T wave are often very similar in Leads aVR and aVL. In SIVB the terminal QRS vector is leftward and superior with good magnitude. The terminal R wave in Lead aVL is relatively tall and significantly exceeds the terminal r (if present) in Lead aVR. No terminal s wave in Lead I is seen with SIVB, and the P wave is rarely inverted in Lead aVL. The ECG in Fig. 12 *A* is a typical example of pseudo-LAD that may be seen with emphysema. The terminal QRS vector is superior and rightward, with a counterclockwise loop. The VCG (Frank lead system) in Fig. 12 *B* shows this loop in the frontal plane. In the horizontal plane the terminal portion of the loop is posterior and relatively rightward. The ECG and VCG are compatible with RVE and pseudo-LAD in a patient with emphysema. If the ECG of a patient with emphysema really resembles that of true LAD and SIVB, additional ischemic heart disease should be considered.

*Superior peri-infarction block (SPIB).* The term "peri-infarction block" was suggested by W. T. McCollum, M.D., University of Oklahoma School of Medicine, and introduced by First, Bayley, and Bedford.[43] These authors' diagnostic criteria of peri-infarction block included: (1) evidence of myocardial infarction of the subendocardial region of the ventricular wall or transmural infarction with a circumferential region of subendocardial damage; (2) QRS complexes in the limb leads which are or exceed 0.11 second in duration; (3) a characteristic QRS pattern in the unipolar precordial and extremity leads. Grant and associates[4,5,6] amplified the concept of peri-infarction with different and more definitive criteria which are: (1) an abnormality of the direction of the initial forces of the QRS interval of a type characteristic of myocardial infarction (accounting for Q waves); (2) an abnormality of the direction of the last forces of the QRS interval so that they come to point opposite to the initial QRS forces; and (3) little or no prolongation of the QRS interval.[4] On the basis of the anatomy of the left ventricle and its conduction system, Grant provided very logical explanations for the left intraventricular conduction defects. These important fundamentals have already been discussed in the *Electropathophysiology* section of this paper. Some authors (Burchell,[44] Pruitt,[44] Castle[7]) prefer the term "post-infarction block" rather than "peri-infarction block." Peri-infarction block is the senior member of the left intraventricular block family and for many years has been such a helpful and faithful friend that we are inclined to stick by it. More importantly, we will *check our premises*. If we adhere to precise rules, recognize the limitations, and place peri-infarction block in its proper clinical perspective, it should continue to serve as a valuable electrocardiographic entity. The rules, limitations, and clinical importance of superior peri-infarction (SPIB) will now be discussed.

Grant[4] raised the question whether a patient with infarction might develop changes in the terminal forces without deformity of the initial forces (no Q waves). At that time he had collected 10 cases of peri-infarction with normally directed initial 0.04 second vectors and autopsy proof of infarction, but a recent preinfarct control ECG was available in none of the cases. We have not seen any cases of peri-infarction block that never had an abnormal initial 0.04 second vector, but we have seen several patients with old infarction proved clinically by previous ECG and/or autopsy who had normal initial forces at some later time. In an ECG with LAD this might occur with: (1) normalization of initial forces with time; (2) electrical neutralization of initial forces by another differently located infarct; and (3) leftward and superior shift of the entire electrical field.[4] If an isolated ECG shows LAD with normal initial forces, SIVB is the best reading, for without control or previous electrocardiograms there is no way of knowing whether the above-mentioned possibilities have been in action or whether infarction or only fibrosis will be found at autopsy. Recent studies[4,73,74] suggest that at autopsy fibrosis is the common denominator in cases of LAD, and that the abnormal initial 0.04 second vector direction of infarction should be required before the term "SPIB" is used. Even then there are limitations for the ECG in patients with

rather marked LVE (especially with aortic valve disease) may resemble that of SPIB and only fibrosis may be found at autopsy. In our study[14] 14 per cent of 302 new cases of LAD in a 5 year period met the criteria for SPIB. Twelve of these patients with SPIB came to autopsy. All 12 were found to have coronary artery disease and fibrosis. A myocardial infarct was found in 9 of the 12 hearts and the other 3 showed rather marked LVE.

We recommend that Grant's original criteria for SPIB be used as follows: (1) true LAD; (2) an abnormal rightward inferior initial 0.04 second QRS vector in the frontal plane; (3) abnormal leftward superior terminal QRS forces in the frontal plane; (4) either normal or prolonged QRS duration due to slowing of the terminal forces. An r′ in Lead $V_1$ or broad slowed terminal QRS forces favor SPIB. Control electrocardiograms and clinical confirmation (history, enzyme rises, etc.) are desirable. In the presence of rather

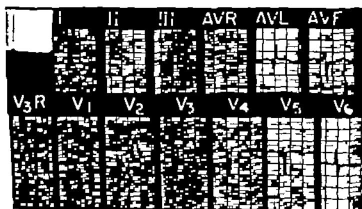



Fig. 13. Seventy-nine-year-old man. ECG demonstrates rightward inferior initial QRS vector, leftward superior terminal vector with ... Lead V ... and LAD—anterolateral superior infarction with superior peri-infarction block (SPIB) and no broadening of QRS.

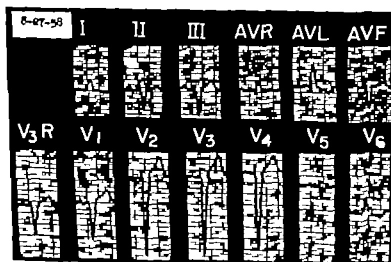



Fig. 14. Eighty-six-year-old man with acromegaly. ECG shows LVE, LAD, and QRS widening due to broad slowed terminal forces not decreasing ... in Lead V ... with W-shaped complex—superior peri-infarction block with QRS broadening. Autopsy revealed an old anterolateral infarction.

marked LVE or cardiomyopathies con servative terminology e g SIVB is often warranted Even if the angle between the initial and terminal QRS vectors exceeds 110 degrees with LAD SIVB is probably the wisest terminology if the initial 0 04 second vector is normally directed

*SPIB* commonly occurs with antero lateral and superior infarctions and less commonly with strictly anterior locations Some patients with pre existing LAD and SIVB may later have an infarction but when there is no control ECG the cause of the LAD (SPIB versus SIVB) may not be determined

The ECG in Fig 13 is an example of SPIB with a normal QRS duration the r in Lead $V_1$ is commonly seen with SPIB *but rarely in SIVB*

The ECG in Fig 14 was recorded on an 86 year old man with acromegaly and LVE clinically The ECG is an example of SPIB with QRS widening and falsely resembles LBBB The q in Lead aVL and the r in Lead III are not quite diagnostically broad but the decrease in r in Lead $V_4$ and the W shaped QRS complex in Lead $V_1$ along with the LAD suggest that this is SPIB and not LBBB The QRS complexes are more likely to be broad and bizarre when LVE and SPIB coexist Autopsy revealed LVE and old anterolateral infarction SPIB has been especially helpful in providing the proper diagnosis and logical explanation for the ECG with LAD and QRS broadening that looked like LBBB LBBB alone does not cause *LAD divergent initial*

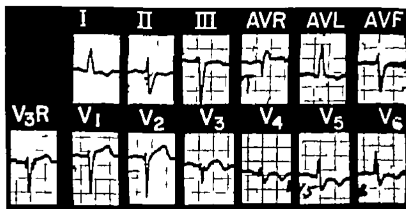



Fig *15* Sixty year-old man ECG illustrates anterior infarction LAD small q in Lead aVL and QRS widening due to broad slowed terminal forces—superior peri infarction block is read as the cause of the LAD because of the terminal slowing of the loop

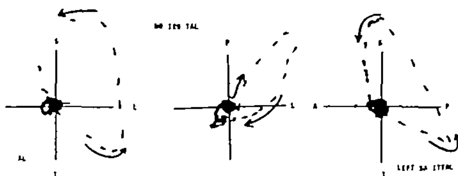
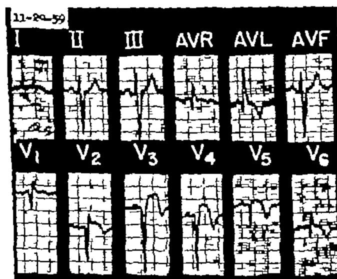


Fig *16* Same patient as in Fig 15 Frank lead system VCG demonstrates the terminal slowing of the loop manifested by an increased number of dots bunched together In the frontal plane LAD with counterclockwise loop is noted In the horizontal plane the clockwise loop is characteristic of anterolateral infarction

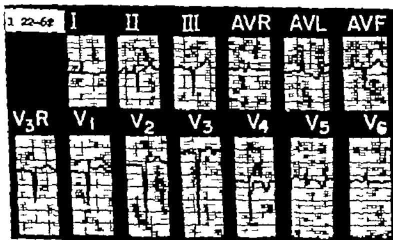
and terminal vectors or slowing of only terminal forces. Past and even recent articles in the literature contain numerous examples of electrocardiograms read as indicating LBBB and infarction that were actually good examples of SPIB *without LBBB*.

In Fig. 15 the ECG shows anterior infarction, LAD, and QRS broadening due to slowing of the terminal forces. In spite of the normally directed initial vector in the frontal plane, SPIB is likely because of slowing of the terminal forces. The VCG in Fig. 16 on the same patient shows this terminal slowing manifested by an increased number of dots bunched together. The clockwise loop in the horizontal plane is characteristic of antero*lateral* infarction.

The ECG in Fig. 17 *A* is an example of acute anterolateral superior infarction with LAD, SPIB, QRS broadening, and r in Lead $V_1$. *The ECG taken 2 years later* on the patient is shown in Fig. 17 *B* and




A




B

Fig. 17. *A*, Fifty-eight year-old man. ECG shows recent anterolateral superior infarction with superior peri-infarction block and some QRS widening. Note r in Leads V... *B*, ECG recorded a little over 2 years later illustrates normalization of the *initial* vector in the *frontal* plane. LAD and r in Leads V... are still present. The anterior component of the old infarct can be seen in Leads V... 

tivity Although inhibition of this enzyme system is well established enzyme activity is affected by changing electrolyte concentration so that changes in the distribution of sodium and potassium by digitalis induced interference with a carrier system might secondarily inhibit the enzyme The fact that digitalis apparently interferes with the flux of substances that are not actively transported such as chloride and of organic molecules such as glucose might support this latter interpretation So would the observation that potassium cannot only obliterate the toxic manifestations of digitalis but can also restore normal activity of membrane ATPase Electrophysiologic studies of the effect of digitalis on the cell membrane are compatible with either hypothesis The demonstration that low doses of digitalis appear to stimulate the enzyme and actually increase the influx of potassium strongly favors a direct effect on the enzyme rather than a mechanism involving competition for carrier sites

Two studies utilizing coronary A V differences have noted that a loss of potassium from the heart is consistently associated with the increased contractility produced by digitalis Furthermore one study indicated that the increase in contractility was proportional to the loss of potassium An analogy has been made with the so called staircase effect in which rapid stimulation of the heart produces progressively more forceful contraction As with digitalis this rapid stimulation is associated with progressive loss of potassium from the muscle presumably due to a reduction in the time available in diastole for re entry of potassium

Despite these observations there is much to suggest that the increased force of contraction produced by digitalis is not related to a loss of potassium There are several experiments in which animals whose heart failure had been compensated by digitalis were then sacrificed They showed no decrease and sometimes even an increase in potassium as compared to the potassium-depleted state associated with congestive heart failure itself Moreover studies of potassium flux and potassium concentration in isolated tissues have produced variable results depending on the tissue and technique used There are many reports that show no change in the concentration or flux of isotopically labeled potassium in ordinary ventricular muscle at therapeutic rather than toxic doses of digitalis

Others report that the effect of digitalis in increasing contractility can be demonstrated before any change in potassium flux or indeed any electrophysiologic evidence of digitalis effect on ventricular muscle can be documented Significant effect on the concentration of potassium in skeletal muscle can be demonstrated without any significant change in the force of contraction Finally the studies which most strongly suggest a close relationship between loss of potassium and contractility have employed coronary A V differences a technique affected by a number of variables and not so reliable as some of the techniques which have failed to show this correlation

*Effects on intracellular calcium* Because of a growing consensus that the inotropic action of digitalis cannot be attributed to its effect on potassium metabolism there has been a search for other possible intracellular changes produced by digitalis that might account for this action It has long been known that an increased concentration of calcium like digitalis has a positive inotropic effect and that the concentration of calcium has at least a permissive role on digitalis induced increased contractility There are several reports of either an increase in intracellular calcium or an increase in calcium flux at therapeutic doses of digitalis there are also studies that fail to confirm this As of this writing it would appear from the literature reviewed that there is probably a small pool of labile calcium whose flux rate is increased by therapeutic doses of digitalis Just how this increased lability of calcium affects contractility is uncertain but certain reasonable possibilities exist The immediate mechanism for cardiac contraction is the sliding and perhaps folding of actin molecules along the myosin molecules resulting in shortening of the sarcomere The energy for this is supplied by ATP [illegible] ich releases its high energy p[illegible] r the [illegible] fluence of myosin A[illegible] latter be found on b[illegible] actin myosin mole[illegible] also

and terminal vectors or slowing of only terminal forces. Past and even recent articles in the literature contain numerous examples of electrocardiograms read as indicating LBBB and infarction that were actually good examples of SPIB without LBBB.

In Fig. 15 the ECG shows anterior infarction, LAD, and QRS broadening due to slowing of the terminal forces. In spite of the normally directed initial vector in the frontal plane, SPIB is likely because of slowing of the terminal forces. The VCG in Fig. 16 on the same patient shows this terminal slowing manifested by an increased number of dots bunched together. The clockwise loop in the horizontal plane is characteristic of *anterolateral* infarction.

The ECG in Fig. 17 *A* is an example of acute anterolateral superior infarction with LAD, SPIB, QRS broadening, and r in Lead $V_1$. The ECG taken 2 years later on the patient is shown in Fig. 17 *B* and

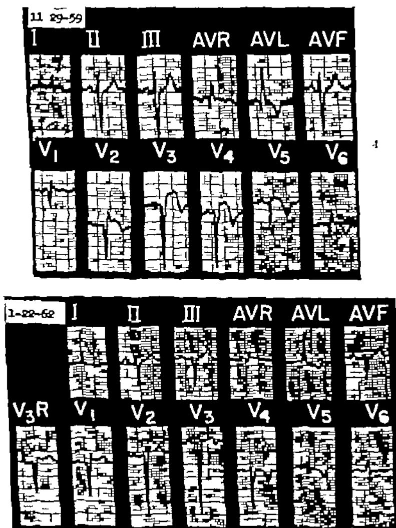
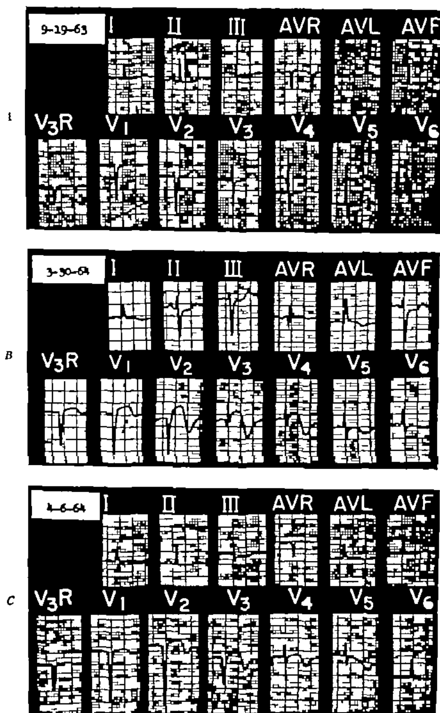



Fig. 17. *A*, Fifty-eight-year-old man. ECG shows acute anterolateral-superior infarction with a infarction block and some QRS widening. Note r in Leads V *B*, ECG recorded a little over illustrates normalization of the initial vector in the frontal plane, LAD and in Leads V. The anterior component of the old infarct can be seen in Leads V $V_3$.

A




B

C

Fig. 18. Forty-nine-year-old woman. *A*, Normal control ECG. *B*, ECG shows acute anterior infarction with LAD and superior peri-infarction block. *C*, One week later ECG shows disappearance of LAD and SI IB. See text for explanation.

some interesting changes are noted The QRS interval has narrowed to a normal duration and the initial QRS vector in the frontal plane has normalized The initial vector in the horizontal plane is still diagnostic of infarction but if the initial vector had also normalized in the V leads, or if only the limb leads were available the etiology of the LAD (SIVB versus SPIB) would not be known al though the r′ in Lead $V_1$ would favor SPIB The presence of LAD in such a case is helpful for it at least points to left ventricular disease

SPIB may occasionally be transient or paroxysmal Fig 18,*A* shows a control ECG The ECG taken on the same patient at the onset of infarction shows acute an terior infarction with LAD and SPIB (Fig 18 *B*) One week later the ECG (Fig 18 *C*) still showed anterior infarction but no LAD Observe the small q in Lead aVL in Fig 18 *B* and its disappearance in Fig 18 *C* This sequence suggests that the infarct blocked conduction through the superior division and forced early initial excitation down the inferior division giving a slightly more inferior initial vector on March 30 1964 (Fig 18 *B*) The dis appearance of the q in Lead aVL and the LAD on April 6 1964 (Fig 18 *C*) indicates that the infarct no longer blocked conduc tion through the superior division and thus allowed simultaneous excitation down both divisions resulting in initial and terminal forces in the frontal plane similar to those of the control ECG in Fig 18 *A* Infarction (anterior or anterolateral) is capable of blocking the superior division proximally near its origin This may be one of the reasons why some authors ob ject to the term peri infarction block ( block causing conduction to go around infarction )

*Congenital heart disease* In the acyanotic patient with congenital heart disease *endocardial cushion defects* are the most common cause of LAD occurring in more than 80 per cent of these patients[4] The LAD in cases of endocardial cushion de fect is not due to LVE but is thought to be due to a congenital abnormality of the conduction system Studies of the conduc tion system in cases of this lesion have shown abnormalities with displacement of the A V node and A V bundle[22,44,47] Fig 19 illustrates a typical ECG of endo cardial cushion defect with LAD and right ventricular enlargement

LAD is seen in slightly more than 15 per cent of all cases of isolated *ventricular septal defects* and it is believed that these defects which cause LAD are of the endo cardial cushion type Abnormalities of the

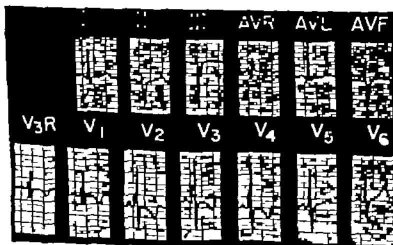



Fig 19 Twelve year-old boy with an endocardial cushion defect ECG demonstrates LAD and right ventricular enlargement (RVE) Note the notch on the S wave in Leads II III and aVF—probably the onset of the influence of right ventricular enlargement on the electrical field This notch is commonly seen with cushion defe

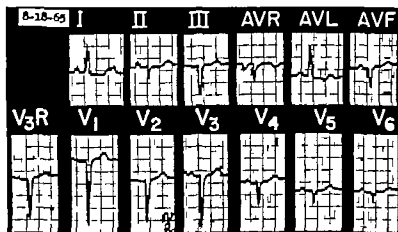



Fig. 20. Twelve-year-old boy with corrected transposition and no other associated defect. ECG shows LAD and rhythm strip recorded runs of 2:1 A-V block.

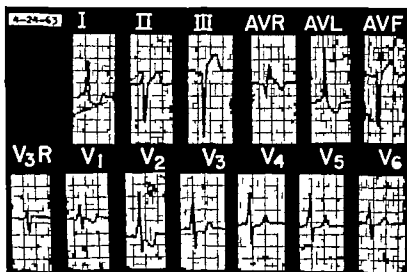



Fig. 21. Twenty-two-year-old woman with Fallot's tetralogy. ECG demonstrates LAD due to the pre-excitation syndrome (type B) which masks the expected RAD and RVE with tetralogy.

conduction system in cases of this lesion have also been demonstrated.[41, 44]

LAD has occurred not uncommonly in *corrected transposition* with left-sided apex, especially in patients with no other associated cardiac defects except frequent A-V block (2:1 or complete).[14] With inversion of the ventricles and the conduction system[14] unusual electrical fields would not be unexpected in these patients. An ECG showing LAD (Fig. 20) and runs of 2:1 A-V block were recorded on a 12-year-old boy with corrected transposition and no other associated defects proved by cardiac catheterization and angiography.

The *pre-excitation syndrome* (*type B*) is an occasional cause of LAD. The ECG in Fig. 21 was recorded on a 22-year-old woman with Fallot's tetralogy and the pre-excitation syndrome with LAD. The expected right axis deviation and right ventricular enlargement are masked by the anomalous conduction.

In the cyanotic group *tricuspid atresia* is the major lesion that causes LAD. In a cyanotic patient if the ECG shows right

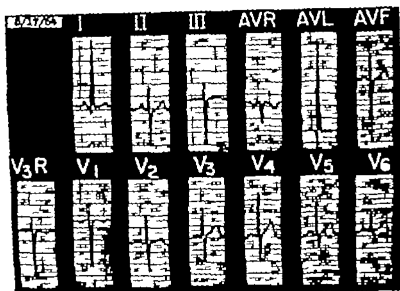



Fig. 22. Six-year-old boy with tricuspid atresia. ECG illustrates LAE, LVE, and LAD.

atrial enlargement (especially with small foramen ovale), left atrial enlargement, no right ventricular enlargement but left ventricular enlargement and LAD, tricuspid atresia will be the diagnosis with rare exception. The ECG in Fig. 22, recorded on a 6-year-old child with tricuspid atresia, demonstrates left atrial enlargement, LVE (35 mm. R in Lead aVL) and LAD.

Slightly over 30 per cent of patients with *single ventricle* will have LAD. Some patients with large complete endocardial cushion defects (A-V communis) will be cyanotic.

LAD has been observed in some very rare forms of congenital heart disease such as *isolated right ventricular hypoplasia*.[3] In *cor biloculare*, right axis deviation is usually present, but 2 cases with LAD have been seen.[33,34]

**Summary**

The anatomy of the left ventricular conduction system and the electropathophysiology of left intraventricular blocks have been presented. Inferior intraventricular blocks have been compared with superior intraventricular blocks.

A new electrocardiographic entity named *left inferior intraventricular block* (IIVB) or parietal block of the inferior division of the left bundle is herein postulated and described.

With rare exception, *true left axis deviation* (LAD) is an abnormal electrocardiographic finding. The most common cause of LAD is *superior intraventricular block* (SIVB) or parietal block of the superior division of the left bundle due to fibrosis caused by ischemic heart disease. Other possible causes of LAD with SIVB are *obscure cardiomyopathies, idiopathic myocardial hypertrophy, scleroderma, cardiac amyloidosis, myotonia atrophica, progressive muscular dystrophy, Friedreich's ataxia, myocarditis, familial cardiomyopathy, hemochromatosis,* and *alcoholic cardiomyopathy*.

*LAD* in the presence of *LBBB* or *RBBB* suggests a more peripheral *SIVB* in addition to the proximal interventricular block.

*Superior peri-infarction block* (postinfarction block) is a senior member of the left intraventricular block family and an important cause of LAD, although it probably occurs somewhat less frequently than was previously thought.

*Hyperkalemia* is presented as a new reversible cause of LAD.

*Surgical injury* to the superior division of the left bundle may cause LAD after operation for congenital discrete fibrous

subaortic stenosis or idiopathic hypertrophic muscular subaortic stenosis

*The pseudo LAD* seen with pulmonary emphysema has been described

In acyanotic patients with congenital heart disease LAD is very common with *endocardial cushion defects* and occurs in slightly more than 15 per cent of all cases of isolated *ventricular septal defects* LAD may be seen in cases of *corrected transposition with left sided apex* especially in patients without other associated defects The *pre excitation syndrome* (*type B*) may cause LAD

In cyanotic patients with congenital heart disease *tricuspid atresia* is the major lesion that causes LAD LAD is present in slightly more than 30 per cent of patients with *single ventricle* Rare forms of cyanotic congenital heart disease that may cause LAD are *isolated right ventricular hypoplasia* and *cor biloculare*

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tivity Although inhibition of this enzyme system is well established enzyme activity is affected by changing electrolyte concentration so that changes in the distribution of sodium and potassium by digitalis induced interference with a carrier system might secondarily inhibit the enzyme The fact that digitalis apparently interferes with the flux of substances that are not actively transported such as chloride and of organic molecules such as glucose might support this latter interpretation So would the observation that potassium cannot only obliterate the toxic manifestations of digitalis but can also restore normal activity of membrane ATPase Electrophysiologic studies of the effect of digitalis on the cell membrane are compatible with either hypothesis The demonstration that low doses of digitalis appear to stimulate the enzyme and actually increase the influx of potassium strongly favors a direct effect on the enzyme rather than a mechanism involving competition for carrier sites

Two studies utilizing coronary A V differences have noted that a loss of potassium from the heart is consistently associated with the increased contractility produced by digitalis Furthermore one study indicated that the increase in contractility was proportional to the loss of potassium An analogy has been made with the so called staircase effect in which rapid stimulation of the heart produces progressively more forceful contraction As with digitalis this rapid stimulation is associated with progressive loss of potassium from the muscle presumably due to a reduction in the time available in diastole for re entry of potassium

Despite these observations there is much to suggest that the increased force of contraction produced by digitalis is not related to a loss of potassium There are several experiments in which animals whose heart failure had been compensated by digitalis were then sacrificed They showed no decrease and sometimes even an increase in potassium as compared to the potassium depleted state associated with congestive heart failure itself Moreover studies of potassium flux and potassium concentration in isolated tissues have produced variable results depending on the tissue and technique used There are many reports that show no change in the concentration or flux of isotopically labeled potassium in ordinary ventricular muscle at therapeutic rather than toxic doses of digitalis

Others report that the effect of digitalis in increasing contractility can be demonstrated before any change in potassium flux or indeed any electrophysiologic evidence of digitalis effect on ventricular muscle can be documented Significant effect on the concentration of potassium in skeletal muscle can be demonstrated without any significant change in the force of contraction Finally the studies which most strongly suggest a close relationship between loss of potassium and contractility have employed coronary A V differences a technique affected by a number of variables and not so reliable as some of the techniques which have failed to show this correlation

*Effects on intracellular calcium* Because of a growing consensus that the inotropic action of digitalis cannot be attributed to its effect on potassium metabolism there has been a search for other possible intracellular changes produced by digitalis that might account for this action It has long been known that an increased concentration of calcium like digitalis has a positive inotropic effect and that the concentration of calcium has at least a permissive role on digitalis induced increased contractility There are several reports of either an increase in intracellular calcium or an increase in calcium flux at therapeutic doses of digitalis there are also studies that fail to confirm this As of this writing it would appear from the literature reviewed that there is probably a small pool of labile calcium whose flux rate is increased by therapeutic doses of digitalis Just how this increased lability of calcium affects contractility is uncertain but certain reasonable possibilities exist The immediate mechanism for cardiac contraction is the sliding and perhaps folding of actin molecules along the myosin molecules resulting in shortening of the sarcomere The energy for this is supplied by ATP which releases its high energy phosphate under the influence of myosin ATPase The latter can be found on bridges between the actin and myosin molecules These bridges also con

tain calcium and magnesium—calcium favors contraction and magnesium depresses it. Since digitalis can be found in this approximate area of the cell it would seem that an action on myosin ATPase similar to its effect on membrane ATPase could well explain its effect. Unfortunately no effect of digitalis on myosin ATPase can be demonstrated. On the contrary there is suggestive evidence that rather than stimulating myosin ATPase directly digitalis acts by interfering with physiologic inhibitors of contraction. A contaminant of artificial preparations of actomyosin was found to be necessary for relaxation of the muscle strip after each contraction. This substance called relaxing factor has been found to be a portion of the invagination of the cell membrane called sarcoplasmic reticulum that surrounds every myofibril. It has a very high affinity for calcium. In the polarized state the relaxing factor and the Z lines contain high concentrations of calcium. With depolarization some of the calcium shifts to actomyosin. Its shift back to the relaxing factor during repolarization permits relaxation. It has been hypothesized that digitalis reduces the affinity of these sites for calcium and thus facilitates mobilization of calcium to actomyosin at the time of depolarization. This change in affinity may be produced by the inhibition of an ATPase but the evidence for this is not clear.

An interesting facet of the inotropic action of digitalis is that it is absolutely dependent on beat—the time of onset of increased contraction is inversely proportional to the heart rate. If cardiac tissue is incubated with digitalis for one half hour and then washed there will be no increase in contractility. How this dependence on beat fits with the effect of digitalis on mobilization of intracellular calcium is yet to be explained.

*Effects on cardiac electrophysiology.* The electrophysiologic effects of digitalis on the other hand would appear to be closely linked to its effect on potassium flux. The direct effects of digitalis on membrane resistance depolarization and repolarization can be well explained mathematically in terms of changes in potassium concentration and flux and the associated changes in sodium. Moreover such electrolyte changes have actually been documented at the time when these membrane changes occur. An apparent paradox exists in that some electrophysiologic changes can occur with low concentrations of digitalis. Yet as mentioned above net loss of $K^+$ cannot ordinarily be demonstrated at full therapeutic levels. The explanation for this paradox lies in the differing sensitivity of different cardiac tissues to the potassium wasting effects of digitalis. When the sensitivity of the Purkinje fiber and that of the ventricular muscle were compared marked changes occurred in the specialized conduction tissue before there was any effect on the ordinary myocardium. The data are less clear for the rest of the specialized conduction system but it is likely that a similar sensitivity is present.

*Effects on other organs.* The effects on the central nervous system are also mediated through a change in sodium and potassium pumping. It is likely that the digitalis effect on peripheral and cardiac nerves is mediated in the same way. Similarly the known important direct effect of digitalis on the kidney is concerned with sodium and potassium transport.

The mechanism of other noncardiac actions of digitalis is more uncertain. Digitalis can interfere with the transport of glucose lysine and other substances in the small bowel. It is uncertain whether these actions are coupled to the sodium potassium pump or represent a direct effect of digitalis on a separate carrier system. Finally there are no data on the cellular basis for the direct effect of digitalis on the peripheral vasculature.

All this suggests that digitalis has two separate effects on the intracellular milieu both of which can be useful in heart disease. These effects would appear to be produced by interference with different enzymes or carriers. Such a dichotomous view of the action of digitalis is not completely satisfying and it has been suggested by some that the two actions are interrelated—that changes in the flux of one electrolyte produces changes in the availability of carriers for other electrolytes. Thus for instance a primary action of the $Na^+$ $K^+$ pump which could be compensated for and be undetectable might lead to measurable changes in calcium lability. Inferential evidence [

## A comparison of the electrical ventricular fibrillation threshold with and without anesthesia

The recent advances in diagnostic, therapeutic, and investigative cardiology have been possible in large part as a result of the increasing use of complex electronic equipment. *However, the use of such* equipment subjects the patient to the very real risk of electrically induced ventricular fibrillation.[1] Studies in this laboratory have emphasized that the danger of causing ventricular fibrillation exists when there is (1) a significant difference in the electrical potential between an electrical source and the heart and (2) when there is a low resistance pathway which allows the delivery of a concentrated current directly to the heart.[1-4] Such a low resistance pathway is possible when the heart is exposed by thoracotomy, when electrode catheters or conventional catheters containing guide wires or needles are introduced into the heart, when needles or small catheters are used for pericardiocentesis, when electrode wires are used for pacing the heart, and during bronchoscopy, tracheal aspiration, gastroscopy, and similar procedures if the instruments used are conductors and come into close proximity to the heart.

It has been shown that 20 microamperes of 60-cycle-per-second alternating current can produce ventricular fibrillation in an anesthetized dog with an electrode *catheter in the right ventricle.* The mean current required to produce ventricular fibrillation on 215 occasions in 20 dogs was 258 microamperes (range, 20 to 800 microamperes). One hundred eighty microamperes of 60-cycle-per-second alternating current produced ventricular fibrillation in an anesthetized human being during operation with the electrodes directly on the heart (mean for 4 patients, 533 microamperes). It has been suggested that such low electrical ventricular fibrillation threshold might exist because of the effects of the anesthetic agent. In order to test the possible *effects of anesthesia on the electrical* ventricular fibrillation threshold, measurements were made in the same animal before and after anesthesia.

A 56-pound mongrel dog was trained over a period of several weeks to remain calm and tolerate a cutdown over the jugular vein. A F 8 electrode catheter was passed to the right ventricle. A 15 square-centimeter stainless steel plate was sutured securely to the shaven left chest near the sternum. Adequate 2 per cent procaine HCl insured freedom *from pain at the cutdown and suturing sites.* Electrocardiographic electrodes were firmly applied to the four extremities. The dog was then placed in a supporting sling. Right ventricular pressure and the electrocardiogram were continuously monitored.

When the pressure and heart rates indicated that the animal was stable, progressively larger alternating currents were passed through the electrode catheter–dog–steel plate circuit for 2-second intervals by the technique previously described. Starting with 50 microamperes, the current was increased by 50 microamperes during successive 2-second periods of stimulation until ventricular fibrillation was induced. Ventricular fibrillation occurred in the unanesthetized dog with a current of 500 microamperes. The animal promptly lost consciousness, and normal sinus rhythm was restored with an externally applied D.C. shock of 200 watt-second. The dog did not appear to suffer any ill effects from the production and conversion of the ventricular fibrillation. He continued to be calm and permitted an intravenous injection of pentobarbital sodium (30 mg. per kilogram) for *general anesthesia. After the right ventricular pres*sure and heart rate had been observed to again be stable for 10 minutes, the procedure as described above was repeated on two successive occasions. The electrical ventricular fibrillation thresholds observed on both occasions were the same as in the unanesthetized state, 500 microamperes.

The results of this study in a single dog are significant in that they indicate that the electrical ventricular fibrillation threshold can be the same in both the unanesthetized and anesthetized animal. It cannot be assumed, therefore, that anesthesia lowers the threshold and makes the animal more susceptible to low levels of current. A repetition of this type of study in the dog that must be trained to accept a fibrillating current would hardly appear to be justified. Similar studies obviously cannot be carried out in man. That the threshold was the same on one occasion makes it mandatory to assume that the electrical fibrillation threshold reported both for the anesthetized dog and man may be valid for the unanesthetized state in both dog and man.

The minimum alternating electrical current that

Supported by Grant HE-0 [illegible] from the National Heart Institute, National Institutes of Health, U. S. Public Health Service.

has produced ventricular fibrillation in the dog is 20 microamperes, that in adult man at open heart surgery 180 microamperes. Whether infants and children have as low a threshold as the dog is unknown. In view of the variability of biologic responses and the potential gravity of ventricular fibrillation, it would appear that any piece of power line-operated equipment used in connection with patients in whom there is a low resistance pathway to the heart should never have a current leak of more than 10 microamperes.

*Henry D. McIntosh, M.D.*
*Frank Starmer, M.S.E.E.*
*Robert E. Whalen, M.D.*
*Cardiovascular Laboratory*
*Department of Medicine*
*Duke University Medical Center*
*Durham, N.C.*

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# A study of the oral flora in children receiving sulfadiazine prophylaxis against rheumatic fever

Continuous chemoprophylaxis against streptococcal infection is recommended to prevent recurrences of rheumatic fever. Statistical studies have demonstrated no difference between the efficacy of orally administered sulfadiazine and penicillin. Penicillin prophylaxis has been shown to alter the oral flora,[19] but comparable studies have not been made in regard to sulfadiazine. This study was designed to evaluate the effect of long-term continuous sulfadiazine prophylaxis on the oral flora.

Twenty-one children from the Grady Memorial Hospital Cardiac Clinics who were receiving continuous sulfadiazine prophylaxis against rheumatic fever as recommended by the American Heart Association for a minimum of 6 months comprised the study group. These children varied in age from 5 to 13 years; there were 7 males and 14 females. No child had received penicillin or other antibiotic for at least 30 days prior to the study. Sulfadiazine had been administered to these children for an average duration of $2\frac{1}{2}$ years, with the duration of prophylaxis varying from 6 months to 6 years.

A control subject was chosen for each child in the study by taking the child of the same sex whose name appeared next on the roll in the patient's class at school; the control subject had received no antibiotic therapy for 30 days prior to the study.

Study of the oral flora was performed in the following manner:

*1. Cultures for alpha streptococci, coagulase-positive staphylococci, neisseria, yeast, and lactobacilli.* The material to be cultured was collected on a cotton swab. The swab was placed in the right upper mucobuccal fold and swept across the mucosa of the cheek to the lower right mucobuccal fold area. It was then carried up the buccal gingiva across the lower right molar teeth and down the lingual gingiva into the floor of the mouth. Maintaining contact with the floor of the mouth, the swab was carried to the left side of the floor of the mouth. It was then carried up the lingual gingiva, across the molar teeth, and into the lower left mucobuccal fold. The swab was swept across the mucosa of the left cheek into the upper fold area, over the buccal gingiva, the molar teeth, and to the palatal area. The child was then asked to extend the tongue while the throat was swabbed with a counterclockwise motion, starting and ending in the left tonsillar area. The swab was placed in BBL 01-604 transport medium and taken to the laboratory for culture.

In the laboratory, the swab was removed from the transport medium with a sterile hemostat and carefully washed in 2 ml. of beef infusion broth. A 0.03 ml. quantity was placed on both a blood agar plate and a tomato juice agar (special) and streaked with the tip of a glass rod. The blood agar plates were incubated and examined after 48 hours. The tomato juice agar plates were examined after 4 days.

The examination of the blood agar plates consisted of: (1) Gross inspection and gram staining of colonies suspected of yielding alpha streptococci, staphylococci, neisseria, and yeast. (2) Alpha streptococci were identified as those colonies which lyse zones of red blood cells immediately surrounding

the colony and composed of chains of gram positi e cocci which were not bile soluble Three colonies on each plate were checked for bile solubility (3) If typ cal staphylococci were found coagulase tests were done Only coa ulase positive taphylococci were tabulated (4) If gram negative diplococci re sembling nei seria were found an oxidase test was done d rectly on the blood agar plate

The examination of the tomato juice agar plate con ted of (1) Gros inspection of the plate with a hand len or wide field microscope for colonies typical of the lactobacillu group (2) Gram staining of se pected colonies for gram positi e diphtheroid like bacilli No attempt was made to confirm them biochemically as lactobacillus

Findings on the cultures were recorded in tabular form thus no colonies few to moderate number of colonies profuse growth of colonies

*2 Smea for fusiform bacill nd spirilla* Material for the smear wa collected w th a sterile wire loop introduced into the gingival sulcus on the lingual a pect of the lower right fir t permanent molar and on the buccal a pect of the lower left first permanent molar Thi material wa diluted in a drop of water and smeared on slide

The smear was stained with cry tal iolet od examined for f iform bacilli and spirilla If only occa ional organisms were seen the lide wa re corded a negativ If organi m were present in large numbers the slide was recorded as positive

It hould be understood that the bov mentioned tests used for identification of the bacteria are by no mean definitive in the sense that biochemical and serologic tudies give conclusive evidence of the identity of a bacterium However it is thought that such presumptive evidence of identification does provide valuable information a long result are interpreted with full knowledge of the limitation imposed

*Table I Alpha streptococci*

| | Sulfadia ine | Control |
|---|---|---|
| No growth | 0 | 0 |
| Moderate growth | 1 | 7 |
| Profuse growth | 20 | 14 |

ALPHA STREPTOCOCCI The cultures for lpha treptococ i were pos ti in all ch ldren in both groups However cultures for 20 of the 21 children in the sulfadia ne group howed a profuse growth of the organi m whereas only 14 of the 1 control cultures howed profuse growth The d ffere ce between th se two groups is gn ficant t the 5 per cent l l (see Table I)

COAGULASE POSITIVE STAPHYLOCOCCI One ch ld in the sulfadiaz group had a mod rat growth of th organ sm in culture The other ch ldren in both groups had negative cultures for coagulase positive staph lococci

NEISSERIA All children in both the sulfadiazine and the control groups had positive cultures for nei seria with no difference noted between the groups

LACTOBACILLI Cultures for lactobacilli showed no significant difference between the sulfadiazine and the control groups (see Table II)

*Table II Lactobacilli*

| | Sulfadia ne | Control |
|---|---|---|
| No growth | 12 | 11 |
| Moderat growth | | 7 |
| Profuse growth | 2 | 3 |

YEAST Yeast cell occurred in equivalent number in the ulfadiazine and in the control groups

FUSIFORM BACILLI AND SPIRILLA Smears for fu form bacilli and pirilla were recorded only as posi tive or negative There was no difference between the lfadiazine and the control groups (see Table III)

*Table III Fusiform bacilli and spirilla*

| | Sulfadia ne | Cont ol |
|---|---|---|
| Positive | 16 | 14 |
| Negative | 5 | |

A d fference in the oral flora between the ulf diaz ne and the control groups was no ed with only one organism the alpha treptococcu A g nificantly increased number of alpha streptococci was present in the oral flora of ch ldren recei ing ulfadiazine proph laxis In thi prelim nary tudy the sensitiv ty of the alpha streptococci to ulfadia ne and other chemoprophylactic agents was not determined Bacterial sen itivity stud es are planned as part of a more exten i survey of the oral flora patients recei ing sulfadiaz ne prophyla a n t rheumatic fever

I summary among 21 child en rece ing long term sulfad zine proph laxis against rheumat c fever the sole diff rence in the oral flora betw en this stud gr up an l the c trol group wa an in creased number of lpha treptococci nificant only t a 5 per cent level There was no gnifica t d fference in the occurrence of coagulase positi taphylococc neisseria lactobacill ea t f f b cill

major alteration in the oral flora was seen to result from sulfadiazine prophylaxis against rheumatic fever

*Annette Anne Wenger M D*
*Frederick Monroe Miller J D D S*
*Uka Brim M S*
*Department of Medicine*
*Emory University School of Medicine*
*Cardiac Clinics*
*Grady Memorial Hospital*
*Emory University School of Dentistry*
*State of Georgia Department of Public Health*
*Laboratories*
*Atlanta Georgia*

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# Sinus tachycardia complicating and outlasting pericarditis

Pericarditis is sometimes associated with sinus tachycardia which bears no relationship to the degree of fever severity of inflammation or congestive heart failure and often persists long after the inflammatory process has ceased.

The rate of sinus tachycardia in 6 cases of pericarditis which I observed ranged from 96 to 130 per minute. In 4 patients pericarditis was part of the postmyocardial infarction syndrome. In the fifth patient there was constrictive pericarditis of unknown etiology. In the sixth case in which chronic pericardial effusion of unknown cause had lasted for many years sinus tachycardia developed shortly after pericardiectomy. It persisted for 4 weeks until corticosteroids were given in an attempt to influence what appeared to be a postcardiotomy syndrome. As to duration sinus tachycardia was present in one patient for a week in another for 4 weeks and in a third for 8 weeks. In the remainder of the patients the duration was 2 months 5 months and 8 months.

Sinus tachycardia was in most instances remarkably constant over periods of several weeks or months. In one patient it was temporarily slowed down by Rauwolfia. In the severest case with sinus tachycardia up to 130 per minute lasting for 8 months, a change to normal heart rate was observed during a short period of hospitalization of this patient but sinus tachycardia returned after discharge. In this particular patient it was possible to slow down the heart rate temporarily by pressure on the carotid sinus area. In another patient who had suffered myocardial infarction there was the appearance of sinus tachycardia which first

aroused su picion of complicating pericardit Th as later substantiated by x ray examination

Recent studies by T N James hed light upon the relation hip of pericardit and the sinus node The uthor pointed out that the sinus node and its nerves because of uperficial position in the heart were commonly invol ed by pericar liti This may result in stimulation of the node and manifest itself in sinus tachycardia or the appearance of various atrial arrhythmia including atrial fibril lation In the aforementioned case n which inu tachycardia lasted for 8 months attacks of atrial fibrillation and frequent trial premature beat ere observed James drew attention to iatrogenic pericarditi brought on by card ac surgery or mas sage of the heart which may manif t itself by the development of various di turbances in rhythm

Knowledge of sinus tachycardia as an innocent complication of pericarditis i mportant because of the grave implication usually associated with this disturbance When seen in conjunction with heart disease sinus tachycardia often con idered to be a sign of severe myocardial involvement or heart failure I a clinical pathologic conference at the Massachusetts General Hospital in which a case of coronary arteriosclerosis w th signs uggesting of pericardial effusion was presented one discus sa t remarked that after subjective and objective improvement a per tent and ominous finding was tachycardia with the rate never dropping be low 104 to 108 per minute Indeed in the first 2 cases which I ob-erved the appearance of inu tachycardia was cause of gra e oncern lest it be indicative of serious myocardial invol ement Later experience did not substantiate th opinion Pa tients with m rked sinu tach rdia did not do worse than other patient uffering from pericarditi without complicating tachycardia E en in the presence of unu ually evere and protracted inus tachycardia the working capacity was trikingly unimpaired

*William Dressler M D*
*Department of Medical Services*
*Maimonides Hospital*
*Brooklyn N Y*

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Address 1150 F fth A New Y k N Y 100 6

## A plea for atrial fibrillation

In addition to their pa ive role as re-ervoir the atria contribute through their contract on to en tricular dynamics It has long been known that atrial systole increases end-dia tolic entricular fill ng and pres ure (provided that the P R interv l is between 100 and 300 m ec ) Thi favors tight closure of the atrio entricular alves and the eby improves stroke olume and cardi output This physio logic dogma has been based h efly upon ex perimental work performed in the animal labora tory Thu every perturbation disrupt ng the re lationship between the atr and the ent cles ad ersely affects performance of the heart as a pump This holds of course for complete A V block Fur thermore countless contemporary pul lication ha stressed the deleterious effect of atri l fibrill tion (AF) on ventricular f ction accor ling to evidence deri ed not only fro a imal experiments but lso from d ta g thered the h man card ac catheterizat on laboratory Consequently it h become commonplace t on ler AF as d tibol cal ent ty nd to l ocate reversion to sinu rhythm (SR) as f damental therapeut mai t This so m sp te of ttered co fli ting st t ent th t ha ppeared in the l terature ex t ly warn g ng that o e enth t iasm t from l bora tory dem onstr tion t real l ai al that sus Not long go the adm tration of q d ne was the method of cho ce for abolishing AF either immediately or more commonly after digitali had lowed the entricular response but failed to re tore SR by tself Succe s w obtained in a fair percent ge of case not infrequently t the cost of d comforting ide effect and occa ionally perilou card ac tox city w th death rat of 3 to 4 per cent Nowaday following the b ic pioneering work of Paul Zoll out t nd ng a h e ements o direct-current countershock ha thoroughly trans formed the que tion By means of th technique of ca d oversio as d scribed by Be nard Low AF can be suppressed with ery low k and tolerable inconvenience t the pat ents With o l ght a toll the growing trend toward broadly ex tend ng nd cat ons for cardioversi o of AF ppears to be understandable and pparently ound

Unfortu tely resto ing SR is but the fir t chapter in a long tory for the main problem still rema ns unmastered that how to l mly prevent recurrence of AF a l pe ma tly maintain the heart under the comma d of the inu nod

Now sever l pos l l t s exist ( ) A fraction of bjects spontaneou ly maint in SR w thout y tifibril tory drug (b) So e others tay SR with mall well tolerated dai l dose f quin d ne (c) But the majority of pat t remain

# Special report

## International Society of Cardiology—The Research Committee at Venice, Italy

*Ancel Keys,* Chairman*
*Research Committee, I.S.C.*

The Research Committee of the International Society of Cardiology (I.S.C.) is charged with the responsibility of informing and extending the activities of the Society in all matters of research relevant to the interests of the I.S.C. At the World Congress of Cardiology in Mexico City, October 1962, it was agreed that the I.S.C., until then concerned almost exclusively with organizing the periodic World Congresses of Cardiology, should be more active in the years between congresses. In particular, it was agreed that the Research Committee of the Society should function between as well as during the congresses.

Accordingly, the Research Committee was reconstituted at Mexico City with 25 members, 3 Corresponding Secretaries, and 3 Liaison Representatives from 22 countries. The officers for 1962-1966 were: Honorary Chairman, Paul Dudley White; Chairman, Ancel Keys; Vice Chairman, Alberto Taquini; Executive Secretary, Jean Lequime. The Research Committee met at Makarska, Yugoslavia, Sept. 18-23, 1963, as reported in various journals (e.g., *British Heart Journal* 26: 556-565, 1964; *Zeitschrift fur Kreislaufforschung* 53: 762-764, 1964; *Japanese Heart Journal* 5: 189-198, 1964; *Acta Cardiologica* 19: 305-320, 1964). The Research Committee met again at the Giorgio Cini Foundation, Venice, Italy, April 11-17, 1965. Notes on the proceedings, currently published in more detail in *Acta Cardiologica*, are given below.

### Venice meeting of the Research Committee

The Venice meeting was attended by representatives from 22 countries and the World Health Organization: 28 members of the Committee and Subcommittees, 14 Consultants, 3 members of the Committee of the 1966 World Congress at New Delhi, and 10 Observers. Items of note included the following.

I. Statement of the I.S.C. for the World Health Assembly (Pierre Duchosal).

II. Report on organization of the World Congress of Cardiology at New Delhi (K. K. Datey, S. Padmavati, Sujoy B. Roy).

III. Reports from Subcommittees of the Research Committee: (a) Epidemiology (J. Stamler); (b) Clinical Physiology (Lars Werko); (c) ECG, VCG, and Computer Applications (H. Blackburn).

IV. Reports on Symposia arranged by the Research Committee to be presented at the Congress in New Delhi (Drs. Henry Blackburn, George Burch, Lewis Dexter, Z. Fejfar, M. J. Karvonen, Kempson Maddox, M. F. Oliver, Otto H. Schmitt, J. Stamler).

V. Report on World Health Organization Activities in Cardiovascular Disease (Geneva HQ—Z. Fejfar; European Office—Z. Pisa).

Received for publication [illegible] 13, 1967.
*Address: University of Minnesota, [illegible] Minneapolis, Minn. 55455.

VI Report from the International Cardiology Foundation (P D White and Howard Sprague)

*I Statement of the I S C for the World Health Assembly* (Pierre Duchosal)

Cardiovascular diseases continue to be major health problems throughout the world They are responsible annually for the disability and death of tens of millions of all ages—children adults in the prime of life and the elderly They place a huge burden on the health services and their drain upon the economy of all countries is continuous and vast

When fully established and manifest clinically as frank illness cardiovascular diseases significantly impair life expectancy All too often they produce sudden and unexpected death Therefore prevention—first and foremost primary prevention also effective secondary prevention based on early detection—is the key to the successful control of the cardiovascular diseases

At present a marked lag exists on a world scale between the acquisition of new knowledge concerning the prevention of cardiovascular diseases and the application of this knowledge in preventive programs Moreover the research effort particularly the epidemiologic research effort—essential for the development of more effective preventive measures—is grossly inadequate in terms both of the need and the potential There is no doubt that a greatly expanded research effort at the international level proceeding first and foremost along epidemiologic lines could be mounted at present and could contribute significantly to early progress in the control and prevention of the major cardiovascular diseases The studies in progress testify to this fact At the same time they demonstrate by their limited nature the large gap between possibilities and actual investigative activities and the major unfilled needs for further research on the epidemiology of cardiovascular diseases and on methodology in this field These unfilled needs reflect inadequacy of resources first and foremost This situation must be a matter of the most serious consideration for all responsible agencies in the field—the International Society of Cardiology the national heart association the World Health Organization and the national health services

In order at the earliest date to overcome present difficulties and to speed up scientific progress and public health advance against the cardiovascular diseases the International Society of Cardiology registers its full support for the proposed W H O International Research Center calls for its earliest possible establishment and urges that it give significant priority to research on the epidemiology control and prevention of the cardiovascular diseases

*II Organization of the New Delhi Congress* (K K Datey S Padmavati Sujoy B Roy)

The Organizing Committee reported that the program for New Delhi adheres to the recommendations endorsed by the Council of the I S C of the Makarska meeting of the Research Committee Plenary sessions with no other competing sessions will occupy the six mornings October 31 November 5 Most of these plenary sessions will consist of symposia presented by invited experts on the subjects proposed by the Research Committee (1) Current Status of the Study of Cardiopulmonary Function (Coordinator J Lequime) (2) Etiology and Pathogenesis of Cardiomyopathies (Coordinator A G Shaper) (3) Present Status of Prevention of Rheumatic Heart Disease (Coordinator R Froment) (4) Precocious Ischemic Heart Disease (Coordinator Kempson Maddox) (5) Evaluation of Cardiovascular and Cardiopulmonary Function After Cardiovascular Surgery (Coordinator Lewis Dexter) (6) Exercise Tests in the Evaluation of Cardiovascular Function (Coordinator M J Karvonen) (7) Computers in Cardiovascular Disease (Coordinator Otto H Schmitt) (8) Effect of Climate on the Cardiovascular System (Coordinator A R Land)

*IIIa The Epidemiology Subcommittee* (J Stamler Chairman)

In various areas of the world there are unique opportunities to study hypertension and coronary heart disease in ethnic groups whose living conditions are changing and who differ in patterns of cardiovascular disease These opportunities continue to be neglected Immediate efforts should

made to explore research potential personnel facilities and financial support in order to improve the situation before irreplaceable opportunities are lost It is proposed that a joint I S C -W H O panel be formed to this end

Current epidemiologic research is providing significant data on the relationship of the incidence of coronary heart disease to several controllable factors the diet cigarette smoking physical activity blood pressure and obesity It is recommended that epidemiologic research on such factors be greatly intensified because of the important potentials for preventive programs

Epidemiologic studies on peripheral vascular disease have lagged and should be encouraged There is need for improved methods for estimating peripheral vascular occlusion and for studies to define relationships between peripheral vascular disease and other circulatory disorders

Epidemiologic research on cerebrovascular disease has also been neglected until recently and even now the efforts are far from commensurate with the importance of the problems The extent to which populations and population groups differ in susceptibility to cerebrovascular diseases is unknown There is a great need for improved methodology especially in the detection of cerebrovascular disease before catastrophic episodes

Epidemiologic information is grossly deficient on chronic respiratory diseases and in the relationship of these disorders to cardiovascular diseases Besides the relative lack of information on these questions there is need for studies on the relative contributions in different populations of chronic bronchitis emphysema asthma recurrent pulmonary embolism and bilharzia Improved objective methods for detection and evaluation of these conditions are needed

In spite of considerable efforts rheumatic heart disease remains a major health problem especially in many parts of Asia Africa and Latin America Further epidemiologic work is needed on the relationship between streptococcal infections and rheumatic heart disease and on the special features in populations in which rheumatic heart disease is common but rheumatic fever apparently is not There is need for more systematic use of the epidemiologic method in the assessment of control programs

Epidemiologic study of congenital heart disease has been neglected There is little information about the extent if any of differences in frequency among populations or on relationships between congenital heart disease and controllable characteristics of the mode of life In this area as in the other areas of circulatory disease noted above it is recommended that epidemiologic research be markedly increased and elevated to a totally new plane

In this whole field of epidemiology much greater support is needed including stable long term financing to obtain basic data to develop improved methods to provide training programs and to expand work directed toward practical problems of prevention In the epidemiology of circulatory diseases medical education is defective there is a major gap between clinical and preventive medicine and there is a marked shortage of trained personnel There is a serious need to develop and support training centers including at least one in a developing country The proposal for an international center under the aegis of W H O is strongly supported Organizations now actively engaged in research on cardiovascular epidemiology should be given support specifically for training both at their home headquarters and in field operations

*IIIb The Subcommittee on Clinical Physiology* (Lars Werko Chairman)

The Subcommittee and its several working groups all emphasized the need for close collaboration with other international organizations with similar or adjacent fields of interest notably W H O the International Physiology Society and the International Biology Program Conferences of small groups on single well defined topics are important and such meetings should be arranged between the large international congresses

The area of responsibility of the Subcommittee on Clinical Physiology is so large that only selected topics were covered at Venice (1) influence of thermal stress on the circulatory system (2) results of cardiovascular surgery (3) influence of exercise on cardiovascular function and disease (4) system analysis in the study of the circulatory system

An *ad hoc* group (L Dexter S B Roy R Margaria) advised that there are many unresolved questions about the circulatory effects of the hypoxia of high altitude and recommended that these be considered in depth on another occasion The Subcommittee noted with satisfaction the activity of the international group on phonocardiography especially on standardization (K Holldack)

1 THERMAL STRESS (George Burch A Sorour M Foor A R Lind)

Cardiovascular responses to thermal stresses pose important problems which warrant much more clinical and scientific attention About two thirds of the world s population is in tropical or subtropical climates but clinical standards in those areas as elsewhere derive from temperate zones Among topics that deserve more discussion and study are cardiovascular problems in acclimatization to cold and to heat cardiovascular problems in acute thermal stress the effect of heat on the hemodynamics of cardiac patients functional capacities of the cardiovascular system in populations living in hot climates regional blood flow in exercise in heat cardiovascular events in heat syncope electrolyte balance in different climates

2 RESULTS OF CARDIOVASCULAR SURGERY (Lewis Dexter John Shillingford Lars Werko)

A panel of eleven cardiologists each from a different country has been organized to make objective evaluations of the results of surgery for specific cardiovascular disorders Arrangements were made for these experts to meet about 6 months before the New Delhi Congress and to present their findings in a symposium at the Congress The disorders to be covered include patent ductus arteriosus constrictive pericarditis and each of the major defects of the valves and septa of the heart In spite of interest in surgery for coronary heart disease and on coronary revascularization it was thought that the time is not yet ripe to make a general assessment of the results of surgery in that area

It was agreed that assessment of both immediate and long term results of cardiovascular surgery requires standardized procedures and recording It is desirable also to determine the change in the natural history of the disease occasioned by surgery It was pointed out that there are striking differences in the severity and complications of these diseases in different parts of the world and allowance for these must be made in assessing the results of surgery

3 EFFECTS OF EXERCISE (M J Karvonen)

The influence of exercise on the cardiovascular system particularly in relationship to the epidemiology of coronary heart disease was selected at the Makarska meeting of the Research Committee as a topic of prime current importance In cooperation with the Finnish Heart Association a special conference of about 80 experts was held at Helsinki August 27 29 1964 the proceedings of that conference are now in press (Charles C Thomas and Company Springfield Ill )

It was noted that lately there is much enthusiastic interest in the possibility of primary prevention of coronary heart disease by physical activity The favorable evidence is largely from statistics on morbidity and mortality among men classified by occupation However interpretation is clouded by occupational mobility and by the inherent obstacles involved in comparing self selected groups There are also questions about differential bias in diagnosis when persons in disparate socioeconomic classes are compared Finally occupational activity does not necessarily reflect total physical activity especially in the developed countries It was agreed that extensive studies more critically designed and carried out are greatly needed in order to assess the possible role of physical activity or a lack of it in the etiology of coronary heart disease Assessment of habitual physical activity is difficult and much needs improvement

In the presence of established cardiovascular disease there is increasing evidence of the value of exercise in rehabilitation However much research is needed to define the exact role of physical activity and to provide appropriate exercise prescription Exercise tolerance tests should be useful in this respect as well as in diagnosis but as yet there is little agreement about the methodology to be used either with patients or in field

Here again much new research is needed

In the meantime there is interest in developing intervention programs involving physical exercise in the hope of preventing coronary heart disease Feasibility studies are needed in order to appraise the possibilities for large scale trials

4 SYSTEM ANALYSIS (Lysle Peterson and an *ad hoc* group with Z Fejfar as recorder)

In cardiovascular clinical physiology there is an important place for system analysis i e the integration of cardiovascular and other functions in the body and the relationships of these with the environment The trend is to put the body together again by the application of computers and related instruments to simultaneously collected data on several or even many variables By these means models of integrated actions may be developed or multivariant analysis can reveal the combined effect of several variables on a single parameter The Research Committee is much interested in these new approaches of system analysis and strongly urges that they be encouraged and made more widely known

*III c The Subcommittee on ECG VCG and Computer Applications* (Henry Blackburn Chairman Pierre Duchosal Noboru Simura Pentti Rautaharju Pierre Rijlant and Consultants Hubert Pipberger and Otto H Schmitt)

Theory based on sound biophysical principles leads to conclusions that restrict or render obsolete some concepts still commonly held in electrocardiography (1) the concept of an absolute zero potential to which ECG leads can be usefully referred (2) the concept of unipolar leads as distinct from bipolar leads (3) the concept that frontal plane Leads I II III or leads derived from them by combinations (VR VL VF aVR aVL aVF) contain intrinsically more information than any pair of them selected at random (4) the concept that the ventricular gradient has a physiological basis rather than being simply an empirical time integral of potential

In ECG techniques much improvement is needed in the skin electrode contact in the recorder in procedural and instrumental standardization in modular design and in quantitative analysis (These points are treated in some detail and recommendations made in the full report pp 17 23 )

Pioneering accomplishments have been made in the application of biophysical concepts and methods to electrocardiography notably in the attempts to provide corrected lead systems in utilization of FM tape recording and in powerful methods of measurement and analysis by computers It is recommended that support be given to the orderly transition into effective application of these new tools It is essential that the new methods retain the contribution to knowledge of the old and during the transition remain as nearly compatible as possible

*II Reports on Symposia*

The Subcommittee reports summarized above cover some of the symposia material arranged for New Delhi Additional symposia sponsored by the Research Committee are noted below

*II a The Cardiomyopathies* (Z Fejfar)

Obscure forms of heart disease notably cardiomyopathies are present in all parts of the world but in tropical and subtropical countries these disorders constitute one of the major clinical and health problems Studies on these questions are in progress in many places but cooperative research should be initiated and such studies need expansion It is recommended that in each cooperating area a cardiac register should be established and the research team should include a cardiologist a radiologist a pediatrician and an epidemiologist Particular attention should be paid to certain groups of patients children pregnant and puerperal women with any suspicion of heart disease persons of any age with pericarditis persons of any age with unexplained cardiomegaly Each cooperating center should establish a serum bank covering all patients with cardiomyopathies

At present population studies on prevalence or incidence of cardiomyopathies are not warranted but field studies would be useful for case finding and for testing certain hypotheses

A symposium on the cardiomyopathies will be held at the New Delhi Congress

*II b Precocious Ischemic Heart Disease* (M F Oliver K Maddox)

In many prosperous areas coronary heart disease in persons under the age of

40 is sufficiently common to constitute a challenge. In order to define more accurately the magnitude of the problem cooperative international studies are needed. Among questions for special study are these: What are the features of the pathology in young patients? Is there any specific anomaly in the anatomy of the coronary system? Is the clinical presentation different from that in older patients? Is the contribution of ischemic heart disease to sudden death the same at different ages? What is the relative importance of different risk factors at different ages?

Although the importance of the prevention of precocious ischemic heart disease was universally accepted, it was thought that more work is required to characterize younger persons at high risk before any large scale international preventive programs are initiated. On the other hand, exploratory preventive trials should be encouraged, especially on young men clinically healthy who appear to be at particularly high risk.

A symposium on precocious ischemic heart disease will be held at the New Delhi Congress.

*IV c. Computer Aided Quantitation* (Otto H. Schmitt)

Comparison of the present state of medical science with electronic and computer technology shows needless disparity. This is in part the result of a series of barriers that must be overcome if medical science is to take advantage of the paths of progress marked out by the physical sciences. These barriers concern: (1) inadequate education both of medical students and of established investigators in mathematics, physics and electronic and computer sciences; (2) the need to move away from attachment to specialized instruments that communicate only to the individual investigator, to system theory and the modular approach; (3) the need to develop sophisticated theory specifically for medical science rather than simply borrowing from available mathematical engineering and biophysical technology; (4) a lag in instrumentation and components for specifically medical purposes because medical science is not investing in the cost of design and development in any way comparable to that of industry and the military in nonmedical fields;

(5) the facing of the standards problem not simply in terms of agreed nomenclature but in terms of preferred values of parameters, formats for tape recording, and in the devices and methods of acquisition of data.

Computer-aided quantitation in regard to cardiovascular function and disease, utilizing properly the advances in the physical sciences, requires that these barriers be appreciated and overcome. A symposium on computers in cardiovascular disease will be held at the New Delhi Congress.

*V. W.H.O. Activities* (Z. Fejfar, Geneva and Z. Pisa, Copenhagen)

Both at Geneva, in the world headquarters of W.H.O., and at Copenhagen, in the European office, activities in the area of cardiovascular diseases are increasing. These activities include the organizing of conferences of experts on different aspects of cardiovascular diseases, stimulation of research programs, preparation of reports and handbooks on problems and methods, coordination of collaborative research programs, and compilation of directories of centers for research and training in the area of cardiovascular disease. There are close official and personal connections between the W.H.O. and the I.S.C.

*VI. The International Cardiology Foundation* (Paul Dudley White, Howard Sprague)

The International Cardiology Foundation is establishing supporting groups in various countries and is becoming more directly affiliated with the I.S.C. A Geneva office, to be established shortly, will strengthen the link between the I.S.C. and W.H.O., as well as emphasize the truly international character of the Foundation. Among other activities the Foundation made possible the Makarska and the Venice meetings of the Research Committee and has greatly helped in the preparations for the New Delhi Congress.

*VII. The Research Committee at New Delhi*

The Research Committee of the I.S.C. will meet at New Delhi on Oct. 29 and 30, 1966, i.e., immediately before the World Congress on Cardiology. Items that may be of interest to the Committee at that time should be transmitted to the Executive Secretary, Professor J. Lequime, 91 Av. Franklin Roosevelt, Brussels, Belgium.

VERHANDLUNGEN DER DEUTSCHEN GESELLSCHAFT FÜR KREISLAUFFORSCHUNG. Edited by Prof. Dr. Rudolf Thauer and Priv. Doz. Dr. Claus Albers. Darmstadt, 1965, Dr. Dietrich Steinkopff Verlag. 394 pages. Price DM 62.

This book is a report of the 31st Meeting of the German Society of Cardiovascular Research, 1965, the main topic of which was cardiac valvular insufficiency. The book includes reports on anatomy, pathology, pathogenesis, hemodynamics, and diagnostic as well as conservative and surgical treatment of valvular insufficiency. Besides these one finds numerous short reports on independently selected topics as well as a chapter containing individual lectures about acute arterial obstruction. Because of the large number of authors the standard of the individual contributions varies. The reports under the main topics provide comprehensive surveys of the pathophysiology as well as clinical and operative indication for and results of surgery using various techniques of aortic and mitral insufficiencies.

MECHANICAL DEVICES TO ASSIST THE FAILING HEART. Proceedings of a Conference. National Academy of Sciences–National Research Council, Washington, D.C., 1966. 287 pages. Price $9.50. (National Academy of Sciences Publication No. 1283.)

This report is the proceedings of a symposium held on Sept. 9 and 10, 1964, under the auspices of the National Research Council and its Committee on Trauma. The symposium is divided into three parts: one concerned with physiology, another with pumps, and the third with cardiac assistance. There are presentations related to oxygenation, left heart assistance with pumps and counterpulsation, experiences with patients, and a description of various types of pumps as well as mechanical and physiologic problems concerned with the use of pumps to assist the heart. This symposium reflects the thinking and progress at the time as well as the depth of the considerations. There are many illustrations and much discussion, but the symposium reveals an inadequate consideration of the basic physiologic, pathologic, and cardiologic problems related to congestive heart failure as well as to the circulation in general. Surely such studies are to be encouraged, but to try these pumps in patients who might continue to live many more months with excellent cardiologic care certainly cannot be accepted by all physicians who have established a close patient-physician relationship. Such aspects of the practice of medicine were not discussed, nor was the extreme importance of the trauma which the major surgical procedures associated with the implantation of such pumps inflicts upon a failing heart. In fact there was an impressive absence of cardiologists and cardiovascular physiologists attendant upon the symposium, thus providing a background of bias. It is well known that major physical trauma and surgery are precipitating causes of congestive heart failure. The role of these procedures and their importance should have received more consideration. The day will surely arrive when the circulation of man can be assisted with benefit, but the symposium will impress the knowledgeable reader with the remoteness of this in spite of recent publicity and sensationalism and the misleading of sick cardiac patients. This symposium is of interest, but those who follow the literature in cardiology will find little new, and the thoughtful reader will be aware of many important problems not considered. Symposia of this sort, a type commonly held in the United States today, do serve a useful purpose, however.

CONGENITAL HEART DISEASE. AN ILLUSTRATED DIAGNOSTIC APPROACH. By Saul J. Robinson, M.D., Clinical Associate Professor of Pediatrics, Stanford University; Herbert L. Abrams, M.D., Professor of Radiology, Stanford University; and Henry S. Kaplan, M.D., Professor, Department of Radiology, Stanford University. Ed. 2. New York, 1965, McGraw-Hill Book Company, Inc. 248 pages. Price $19.50.

This is the second edition of a book first published in 1954. The current edition represents a moderately extensive revision and amplification. The book is presented in two sections. The first deals with clinical evaluations, routine and special laboratory procedures, and treatment of congenital heart disease in general. The second section is in atlas form and covers the specific congenital cardiac defects.

It is difficult for this reviewer to make a recommendation to potential readers regarding this relatively short book. It is unclear which group stands to profit from the material presented here. It is obviously not for the cardiologist or for the internist seriously oriented toward cardiology. To other groups with an interest in congenital heart disease there may be something of value. For them the book would provide a concise and lucid but not profound review of the problem. Particularly valuable is a short but well-chosen bibliography.

THE PATHOGENESIS OF CARDIAC CACHEXIA By Joseph G Pittman M D Research Fellow in Medicine Massachusetts General Hospital nd Harvard M dical School and Ebin Cohen M D Associat in Medicine Peter Bent Brigham Hospital and Harvard Medical School Boston Mass New York 1965 Grune & Stratton Inc 88 page Price $5 25

Th book focu es attention on the pathogenesi of the cachexia that often accompanies chronic long stand ng congestiv heart failure The in creas ng importance of thi relatively neglected clinical probl m is underscored by recent medical nd surgical adv nces in the treatment of heart d sease which have prolonged considerably the lives of ma y cardiac patients Dr Pittma and Dr Cohen describe the pathogenesis of cardiac cachexia in term of dietary factors metabolic abnormalitie a ociated with conge tive heart failure abnormal losses of nutrients and iatro genic factors These contributory cau es are the subject of detailed analysis in thi carefully written and exten ively documented monograph Therapeutic problems are considered only ery briefly

PAIN IN THE CHEST B William H Wehrmacher M D F A C P F A C C Northwestern Uni versity Medical School Chica o Ill Springfield Ill 1964 Charles C Thomas 403 pages Price $14

Problem in the differential diagnosis of chest pain are the subject of detailed discussion in this highly readable book Dr Wehrmacher rightly emphasizes the fact that in mo t instances the et ology of chest pain can be establi hed on the ba of a meticulous and systematic cl cal history and phy ical exam nation supplemented by a few relatively simple laboratory studies The book divided into two ections the first of which describes specific applications of the techniques of cl nical examination and laboratory procedures to the evaluation of chest pain The second ection is devoted to clinical pathologic and therapeutic considerations of the various cause of chest pain which is classified according to anatomic origin including pain orig nating in structures of the thoracic w ll thoracic vi cera medias tinum shoulder girdle head neck and abdomen and from a number of miscellaneou syndromes that ha e no topographic localization The material is presented in a conci e manner with empha is on condition that are either un *familiar or likely to be overlooked b diagno ti cians*

Thi i a valuable book for physicians and medical students

## Books received

REPRODUCTION MOLECULAR SUBCELLULAR AND CELLULAR Ed ted by Michael Locke New York 1966 Academic Press Inc 344 pages Price $11 50

PRINCIPLES OF HEMATOLOGY By J me W Linman New York 1966 The Macmillan Co 671 page Price $12 50

ADVANCES IN RESPIRATORY PHYSIOLOGY Edited by Colin G Caro Baltimore 1966 The Williams & Wilkins Company 348 pages Price $17 50

American Heart Journal

*October 1966 Volume 72 Number 4*

# Editorial

## Coronary arteriography

*Richard S. Ross, M.D.*
*G. C. Friesinger, M.D.***
*Baltimore, Md.*

The contributions of many, but especially those of Mason Sones,[1] have made it possible to obtain excellent visualization of the coronary arteries in conscious man under circumstances which are close to physiologic normality. Adequate visualization of the coronary tree requires multiple selective injections of the coronary arteries with the patient in different positions. Visualization after the administration of a coronary vasodilator is also helpful. Highly specialized radiologic and photographic equipment is required, and both professional and technical personnel must be well trained.

Radiologic and photographic techniques have improved progressively, and relatively minor anatomic lesions can now be detected; hence problems of interpretation have now assumed great importance. The significance of arteriographic findings depends to a large extent upon the population under study, and this in turn depends on indications for study. For this reason it is worth while to consider the indications which are currently employed in most laboratories. The majority of the patients subjected to coronary arteriography fall into two groups on the basis of indication for study. The first group of patients commonly studied (in 1965) are those who have typical angina pectoris which is disabling and unresponsive to medical therapy. These patients are studied to select those who may be helped by surgical therapy. The second group of patients have chest pain which is not typical angina pectoris, and which therefore is of uncertain origin. In this editorial we are concerned with patients in this second group in whom the arteriography is being performed as a diagnostic test.

One of the problems in the interpretation of the coronary arteriogram as a diagnostic test appears to stem from an imprecise definition of terms. The authors think that the diagram in Fig. 1 is useful in defining

From the Department of Medicine and R[illegible], The Johns Hopkins University School of Medicine and The Johns Hopkins Hospital, Baltimore, Md.
Supported by [illegible] Public Health Service Research Grant No. HE-[illegible] and The [illegible] Grant No. FR 35 from the Division of General Medical Sciences, United States Public Health Service.
Received for publication Dec. [illegible] 1965.
Rec[illegible] of [illegible] Career Development Award No. [illegible]. Address: The Johns Hopkins Hospital, Baltimore, Md. 21205.
**Clayton Scholar.

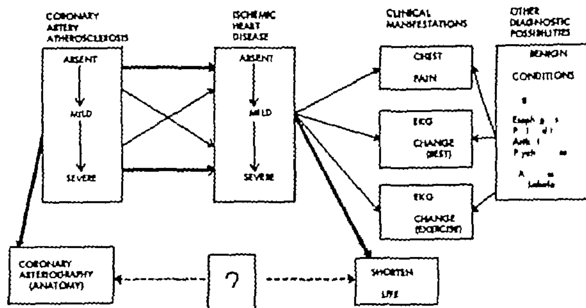



Fig. 1. Diagrammatic representation of the relationship between coronary artery atherosclerosis and ischemic heart disease. The clinical manifestations of ischemic heart disease which usually result in the patient's presentation as a diagnostic problem are also listed.

terms and outlining the problems posed by the patient who may have ischemic heart disease. The essential feature of the problem is the separation of *coronary artery atherosclerosis* from *ischemic heart disease* as indicated by two blocks on the left hand side of the diagram. Coronary atherosclerosis is a disease process involving the coronary arteries. It may be mild, severe, or absent. In Americans and most other Western people it is regularly present in adult males, progresses predictably with advancing age, and has a propensity to localize in certain areas of the coronary tree.[4] This pathologic process in the coronary arteries is usually, but not always, responsible for ischemic heart disease.

Ischemic heart disease is defined as the disease of the myocardium which usually develops as a consequence of coronary atherosclerosis and declares itself clinically by the development of angina pectoris, myocardial infarction, or electrocardiographic changes. The most important of all the manifestations of ischemic heart disease is its propensity to shorten life, and this aspect of the disease justifies all the thought and study devoted to it in recent years.

Let us examine the relationship between coronary atherosclerosis and ischemic heart disease as depicted in Fig. 1. If there is no coronary atherosclerosis, there will be no ischemic heart disease. If at the other extreme there is severe coronary atherosclerosis, ischemic heart disease will usually, but not always, be present. Thus at the extremes of the spectrum a good relationship exists between the degree of coronary atherosclerosis and the presence of ischemic heart disease, as indicated by the heavy arrows in the figure.

The patient usually is referred for evaluation because of chest pain or another clinical manifestation (Fig. 1) which may be due to ischemic heart disease. The diagnostic problem arises because the clinical manifestations are not easily identified with certainty as being due to ischemic heart disease. One or more of the conditions indicated as "benign" may be responsible. The physician needs to know whether the clinical manifestations are related to ischemic heart disease, which will shorten the patient's life, or to a benign condition which will not influence his longevity. Although arteriography is performed to determine whether the patient has ischemic heart disease, the study can only provide information about the

anatomy of the coronary arteries and the extent of the atherosclerotic process and does not directly detect or quantitate ischemic heart disease

A consideration of the sensitivity of the arteriographic method is essential to any discussion of interpretation The degree of atherosclerotic disease which need be present to be detected arteriographically in intact man has not been defined precisely but available data indicate that luminal narrowing of 20 per cent will go undetected and more severe degrees of reduction in vessel size may not be appreciated if such narrowings are circumferential cylindrical and smooth[5,6]

The arteriographic findings to be expected and the interpretation of the arteriogram will be importantly influenced by the population selected for study Age is an important factor It has been demonstrated that histologic changes of coronary atherosclerosis are frequently present in young adult males[3] However postmortem correlation of the histologic and arteriographic findings suggests that appreciable arteriographic alterations in asymptomatic individuals under 45 to 50 years of age must be very uncommon[7] In addition postmortem studies have shown the pathologic changes in the coronary arteries to be regularly severe and multiple when ischemic heart disease is present[7,8] Hence an arteriographically normal coronary tree is very strong evidence against the presence of ischemic heart disease in this age group (under 50) Conversely the atherosclerotic alterations seen in a large segment of the population over 60 years of age make it hazardous to attribute complaints of atypical chest pain to ischemic heart disease in a patient in this older age group who is shown to have minor abnormalities Typical angina pectoris is regularly associated with severe pathologic changes and the instances in which the arteriogram did not disclose prominent changes in individuals with classic angina pectoris have been very rare in our experience Similarly we have never failed to demonstrate changes on the arteriogram of individuals with a history of myocardial infarction and residual electrocardiographic changes Arteriographically normal coronary vessels have been demonstrated in individual with a good history of a myocardial infarction with accompanying enzymatic alterations but without permanent electrocardiographic changes or the development of angina pectoris We suspect that such individuals are unusual but are convinced that we have studied three such cases We presume that these patients either experienced a twig thrombosis in the absence of diffuse and or severe disease or occluded and then totally recanalized a larger vessel The latter possibility seems to be the least likely The prognosis in these cases is probably good

With these observations in mind let us look again at the schematic representation in Fig 1 The bold arrows connecting coronary atherosclerosis and ischemic heart disease indicate the usual relationships at the extremes of the spectrum The thin arrows indicate that other relationships are possible as suggested by the experience cited above For example severe ischemic heart disease as evidenced by a myocardial infarction can result from atherosclerosis which is arteriographically mild on the other hand it is possible that severe atherosclerosis can be present and not result in ischemic heart disease if there are adequate collateral channels

Coronary arteriography is most useful when it is used in conjunction with other methods of evaluation of the patient with chest pain Most important in this regard is thoughtful and detailed and usually repeated history taking in difficult cases In addition exercise electrocardiography as outlined by Sheffield and Reeves is a useful adjunct Although resting electrocardiographic changes may be the result of some of the benign conditions confused with ischemic heart disease a truly positive ischemic electrocardiographic response to exercise has few if any other explanations The combination of a normal coronary arteriogram and a negative exercise test makes it extremely remote that the patient s complaint of recurrent chest pain is attributable to ischemic heart disease

The physician s duty extends beyond the exclusion of ischemic heart disease as a source of the patient s pain to the identification of the true cause of the symptoms Esophagitis commonly produces symp

toms that are confused with those of ischemic heart disease but it is only one of a long list of diseases which constitutes the differential diagnosis of chest pain. Prominent on this list is cardiac neurosis which is prone to become established because of the long duration of the complaints, the contact with many physicians and the inability or unwillingness of physicians to take a firm stand.

The diagnostic value of coronary arteriography will be enhanced by the completion of studies currently in progress which are designed to correlate the arteriographic findings with clinical manifestations and duration of life. Such correlations will bridge the gap between the arteriogram which quantitates coronary atherosclerosis and manifestations of ischemic heart disease which are of clinical importance.[1] An example of such a study is seen in Table I which shows the results of our experience correlating the type of chest pain with arteriographic findings. All patients were referred for evaluation because one or more physicians had made a diagnosis of ischemic heart disease. It is to be noted that the majority of patients with typical angina pectoris have severe degrees of coronary artery atherosclerosis. At the other extreme, when the pain is clearly not angina pectoris, a positive arteriogram is unusual. The arteriogram makes its major contributions in the group with atypical chest pain. These patients who have at least one feature of typical angina pectoris but not all three features are found to have arteriograms that range from revealing complete normality to showing the most severe atherosclerosis. Thus it is in this group that the arteriogram is helpful in identifying patients with severe disease who on the basis of history alone are indistinguishable from those with minimal or no disease. It is incorrect to assume that because the pain is atypical any coronary disease which is present will be of minor degree. The completed analysis of a larger experience will hopefully make it possible to define the minimal arteriographic lesion which can be responsible for significant symptoms of ischemic heart disease.

The most important and significant manifestation of ischemic heart disease, its tendency to shorten life, should be a factor which correlates with coronary arteriographic findings. We are making a study of such correlation. The goal of this study will be the development of tables which can be used to estimate the duration of life of a patient with a given arteriographic finding. Such an analysis may be the only means by which therapeutic maneuvers can be adequately assessed. Actually, it is widely appreciated that there may be no means by which therapy can truly be evaluated in patients with ischemic heart disease in whom the propensity to develop a collateral circulation is so unpredictable and yet so critical in determining prognosis. Data relating the arteriographic findings, including the presence of collateral vessels, to the prognosis

Table I

| Pain | Arteriographic class | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 |
| Typical angina pectoris | 7 | 0 | 5 | 11 | 31 |
| Atypical angina pectoris | 6 | 4 | 4 | 5 | 6 |
| Uncertain pain | 4 | 4 | 1 | 1 | 1 |
| Not angina pectoris | 19 | 4 | 1 | 1 | 0 |

Arteriographic classification
0 Normal arteriogram
1 Minimal abnormalities
2 Single narrowing > 50 per cent
3 Multiple severe narrowings > 50 per cent
4 One or more total obstructions

Pain classification
Typical angina pectoris: Pain which is
(1) Clearly precipitated by exertion and relieved by rest
(2) Deep visceral pain described as heavy, squeezing, a burning, etc.
(3) Involves some portion of the sternum

Atypical angina pectoris: Pain which has one or two but not all three of the properties of typical angina pectoris as described above but which all physicians believe to be of ischemic origin

Not angina pectoris: Pain which two clinicians agree is not angina pectoris

Uncertain pain: Pain which the clinicians could not classify into any of the three groups, or about which two clinicians disagree

in individuals who have not received any specific form of therapy will certainly be the only means of assessment of a variety of surgical techniques which are currently being tried The surgical procedures may relieve symptoms but if they are truly improving myocardial circulation they should increase life expectancy

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# Clinical communications

## Isolated abnormalities in high precordial leads, an infrequent sign of myocardial infarction

*Morton Lee Pearce, M.D.**
*Warren Kossowsky, M.D.*
*Raphael Levine, M.D.*
*Los Angeles, Calif.*

In 1946 Rosenbaum, Wilson, and Johnston[1] suggested that unipolar leads from the high left thorax be taken when Leads I or aVL suggest a myocardial infarction but the 6 standard precordial leads fail to demonstrate the expected QRS changes. Other workers[2-4] have also made this suggestion, but in their studies, as in those of the Wilson group, anatomic confirmation of the electrocardiographic diagnosis of high lateral infarction has been infrequent.

The purpose of this report is an evaluation of the usefulness of high precordial leads in establishing a diagnosis of high lateral infarction in patients whose limb leads (I or aVL) suggest this possibility but whose standard precordial leads do not confirm the diagnosis. The study is based on 20 patients whose electrocardiograms met these criteria and who later came to autopsy.

### Methods

Since 1959, all patients with a conspicuous Q wave in Leads I or aVL of the conventional 12 lead electrocardiogram have had an additional 6 chest leads taken two intercostal spaces above the conventional leads. We have found that the complexes recorded from these positions are reproducible in the hands of our technicians. All electrocardiograms were taken with a direct writing electrocardiograph at a paper speed of 25 mm. per second. Two hundred and eighty-six of these patients have come to autopsy; 20 of these had Q waves in Leads I or aVL which were not present in the standard precordial leads and Q waves in their high precordial leads. Since one of the two patients with infarction had only an isolated QS of 0.08 second in the high $V_3$ lead, a QS or QR with a 0.04 second Q wave in the high $V_3$ lead or lateral to it were the minimal criteria for inclusion.

### Results

Of the 286 autopsied patients reviewed, 20 displayed the expected QRS changes of infarction in the high precordial leads without demonstrating any diagnostic abnormality in the standard precordial leads.

In 18 of these 20 cases the electrocardiographic diagnosis of infarction could not be substantiated at autopsy. Two cases

From the Veterans Administration Center, Los Angeles, Calif., and the Department of Medicine, University of California Center for the Health Sciences at Los Angeles, Los Angeles, Calif.
Received for publication Dec. 16, 19[illegible].
*Address: Veterans Administration Center, Wilshire and Sawtelle Blvd., Los Angeles, Calif. 90073.

Table I Descriptions of leads I aVL and high precordials in 18 patients without infarction and in 2 patients with infarction

| Serial number | I—I | I—aVL | Duration Q—I | Depth (mm) Q—I | Duration Q—aVL | Depth (mm) Q—aVL | I—I | I—aVL | High precordial leads $V_1$ | $V_2$ | $V_3$ | $V_4$ | $V_5$ | $V_6$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Eighteen patients without infarction | | | | | | | | | | | | | | |
| 1 | ↑ | ↓ | — | — | 0.04 | [illegible] | ↓ | ↓ | QR | QR | QI | qR | qR | qR |
| 2 | ↑ | ↓ | — | — | 0.04 | 1 | ↑ | ↓ | QS | QS | QS | QS | qRS | Rs |
| 3 | ↑ | ↓ | 0.02 | 0.25 | 0.03 | 1 | ↑ | ↑ | Qr | QS | QS | qRS | Rs | R |
| 4 | ↑ | ↓ | 0.02 | 0.25 | 0.09 | 2.5 | ↑ | ↑ | QS | QS | QS | QS | QS | qRs |
| 5 | ↑ | ↓ | 0.01 | 0.25 | 0.03 | 1 | ↑ | ↓ | Qr | QS | QS | qrS | qRs | qRs |
| 6 | ↑ | ↓ | 0.0[illegible] | 0.5 | 0.07 | 1.5 | ↓ | ↓ | QS | QS | QS | QS | qrS | qR |
| 7 | ↑ | ↓ | — | — | 0.03 | 1 | ↓ | ↓ | QS | QS | QS | qrS | qRS | qRS |
| 8 | ↑ | ↓ | 0.02 | 1 | 0.03 | 1 | ↓ | ↑ | — | — | rS | qrS | qRs | qR |
| 9 | — | — | 0.02 | 0.25 | 0.05 | 1.5 | ↓ | ↓ | rS | Qr | Qr | Qr | QrS | qRs |
| 10 | ↑ | ↓ | 0.0[illegible] | 0.5 | 0.05 | 1 | ↑ | ⇅ | rS | Qr | QS | qRs | qR | qR |
| 11 | ↑ | ↓ | 0.02 | 0.5 | 0.03 | 2 | ↑ | ↓ | Qr | Qr | Qr | QRs | qR | qR |
| 12 | ↑ | ↓ | — | — | 0.04 | 1.5 | ↑ | ↑ | QS | QS | QS | qR | qRs | qRs |
| 13 | ↑ | ↓ | 0.02 | 0.5 | 0.03 | 1 | ↑ | ↓ | QS | QS | QS | qRs | qR | qR |
| 14 | ↑ | | — | — | 0.06 | 2 | ↓ | ↓ | rSr | rSr | rSr | QS | qRs | qR |
| 15 | ↑ | ↑ | 0.03 | 1 | 0.04 | 1.5 | ↑ | ↑ | qrS | qRs | qrS | qRs | qR | qR |
| 16 | ↑ | ↑ | — | — | 0.03 | 1 | ↑ | ↓ | QS | QS | QS | rS | Rs | Rs |
| 17 | ↑ | ↑ | — | — | 0.02 | 0.5 | ↑ | ↑ | — | Qr | QR | qR | R | R |
| 18 | ↑ | ↑ | — | — | 0.02 | 0.5 | ↑ | ↑ | QS | QS | QS | QRS | qRs | qR |
| Two patients with infarction | | | | | | | | | | | | | | |
| 1 | ↑ | ↑ | — | — | Tiny notch | | Flat | ↑ | QS | QS | QS | QS | rS | rS |
| 2 | ↑ | ↓ | 0.02 | 0.5 | 0.01 | 1 | ↓ | ↓ | QS | QS | QS | qRS | qRS | qRS |

showed changes in the high precordial leads which were not seen in the conventional chest leads and had infarcts. One of these two had 0.02 second Q waves in Leads $V_{4-6}$ which were 1 *mm.* deep followed by sharp R waves. The high precordial leads showed 0.09 second QS waves in Leads $V_1$. Autopsy revealed an extensive anterior infarct from the base to the apex extending into the lateral wall. The posterior surface showed patchy fibrosis. In the second case there were no Q waves in the standard precordial leads although the high precordial leads showed a QS in Leads $V_{2-4}$ and a 0.02 second Q wave in Leads $V_{4-6}$ less than 0.5 mm. deep. There was a 2 cm. subendocardial infarct high on the anterior wall. Electrocardiographic Leads I, aVL, and the high precordial leads are described in Table I.

The electrocardiogram of one patient who had a high anterolateral infarct at autopsy showed a left ventricular conduction defect, and Q waves were not present in the standard or high precordial leads.

### Discussion

Rosenbaum, Wilson, and Johnston[1] reported 6 cases of suspected infarction of the basal parts of the lateral wall of the left ventricle in which the conventional 12 lead electrocardiogram failed to establish definitively a diagnosis of myocardial infarction but in which unipolar leads from points on the anterolateral, lateral, and posterolateral aspects of the upper left thorax supplied ECG data of greater diagnostic value. There was no autopsy confirmation in any of these cases.

In a later communication[2] these same authors stated that the electrocardiographic pattern of high anterolateral wall infarction shows diagnostic changes in Leads I or aVL and in unipolar leads from *parts of the left side of the precordium or* of the anterior surface of the left side of the chest that are nearer the left shoulder than those from which Leads $V_4$, $V_5$, and $V_6$ are taken. The complexes of some of the standard leads from the left side of the precordium are abnormal but show much less pronounced changes than those exhibited by the *leads mentioned.*

In 1949 Myers and associates suggested that infarcts confined to the anterior, lateral, and posterior aspects of the base of the left ventricle which could not be recognized by employing the standard *Wilson leads could be recognized by using* high thoracic leads. These authors reported 14 cases of autopsy-proved high lateral infarction. The infarct was subepicardial in one case, transmural in 5, and *subendocardial in 8.* High leads at the level of the third intercostal space were obtained in 4 patients who were followed to autopsy, and in one case the high precordial leads showed a diagnostic Q wave *not seen in the standard precordial leads.*

Further support for the use of high leads was given when Prinzmetal, Kennamer, and Massumi[7] studied the high chest leads in a large number of normal subjects and in 66 patients with myocardial infarction, and reported 6 instances in which the use of the high leads helped to establish the diagnosis of infarction. Again in these cases there was no autopsy confirmation.

Roesler[4] suggested that T wave changes in the high precordial leads might be of value in the diagnosis of *minor infarctions* and Singer[3] reported 3 cases of high infarction with changes in high precordial leads which were not seen in the standard precordial leads, including one case substantiated at autopsy.

Our own data suggest that high precordial leads are of little value in the diagnosis of infarction, and that the electrocardiographic changes are usually due to other causes. Rosenbaum, Wilson, and Johnston[1] thought that the electrocardiographic changes were usually due to in*farction of the parts of the wall of the left* ventricle which are closer to the base of the chamber than those more commonly involved, but did suggest that the abnormalities are sometimes the result of *rotation of the heart or of some other* change in the spatial relationships of its surface to the standard electrocardiographic leads. It should be noted that our 18 patients without infarction do not represent a normal population. Most of them were elderly men with a variety of illnesses. Prinzmetal and co-workers[7] studied *a normal population* with high leads from $V_1$ through $V_6$ and found that Q

waves were rare in the high $V_2$ through $V_4$ positions.

This study suggests that infarction of the base of the left ventricle is the exceptional reason for the electrocardiographic abnormalities noted with the use of high precordial leads when the standard precordial leads fail to show them.

**Summary**

The electrocardiograms of 286 autopsied patients with Q waves in Leads I or aVL who had high precordial leads taken were reviewed. Twenty patients displayed QRS changes of infarction in the high precordial leads without demonstrating any diagnostic QRS changes in the standard precordial leads. In only two instances was the electrocardiographic diagnosis supported at autopsy. It is suggested by this study that myocardial infarction is the exceptional cause for the electrocardiographic abnormalities seen only in the high precordial leads.

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# Accuracy of preoperative diagnosis in congenital heart disease

*Carlos Pestana, M.D., Ph.D.**
*William H. Weidman, M.D.***
*H. J. C. Swan, M.B., Ph.D.****
*Dwight C. McGoon, M.D.*****
*Rochester, Minn.*

Successful cardiac surgery depends to some degree on a correct preoperative diagnosis. However, many inaccuracies in the diagnosis can be discovered at operation by the experienced surgeon and the proper repair completed with minimal or no inconvenience to the surgeon or increased risk to the patient. On the other hand, certain errors in preoperative diagnosis can have a catastrophic effect on the outcome of an operation. This study was undertaken to evaluate the accuracy of the preoperative diagnosis of the condition of patients undergoing cardiac surgery for congenital defects and to determine the incidence of errors that significantly affect the success or safety of cardiac surgical procedures.

## Method

We reviewed the records of all patients having a final surgical diagnosis of congenital heart disease who were operated on at the Mayo Clinic from July, 1963, through June, 1964, a total of 358 patients. Special attention was paid to diagnoses made after cardiac catheterization performed elsewhere and after clinical evaluation and cardiac catheterization performed at the Mayo Clinic. We shall use the term "clinical diagnosis" to designate the diagnosis made from the history, physical examination, roentgenograms, and electrocardiograms but without the benefit of cardiac catheterization.

Of the 358 patients, 162 had been referred to the Mayo Clinic with a diagnosis that had been established elsewhere by cardiac catheterization. Since these patients represent a heterogeneous group in which the indications for and technique of cardiac catheterization were not uniform, they will not be discussed in detail.

The other 196 patients, who had not had a cardiac catheterization previous to their visit to this clinic, provide the material on which our results are based. Their ages ranged from 10 days to 65 years.

## Results

The 196 patients were divided into three groups. The first group comprised 106 patients (54 per cent) for whom operation was advised on the basis of clinical diagnosis only. Cardiac catheterization was

Received for publication Dec. 20, 1965.
Read in ... Mayo Graduate School of Medicine (University of Minnesota), Rochester, Minn.
**Section of Pediatrics, Mayo Clinic and Mayo Foundation.
***Section of Physiology, Mayo Clinic and Mayo Foundation.
****Section of Surgery, Mayo Clinic and Mayo Foundation. Address correspondence to ... Section of Publications, Mayo Clinic, Rochester, Minn. 55901.

not considered to be necessary for the establishment of a diagnosis in these cases although such a study was carried out in 22 of them in order to obtain supplemental information relative to physiologic or anatomic variables. Patients were retained in this group even if subsequent catheterization established an additional or alternative diagnosis and in this paper and its tables the diagnosis established before catheterization was retained as the preoperative diagnosis. The second group comprised 60 patients (31 per cent) for whom the clinical diagnosis was somewhat insecure and cardiac catheterization was considered to be necessary to establish the diagnosis. The third group comprised 30 patients (15 per cent) for whom a plausible clinical diagnosis could not be made and diagnosis was attempted only after cardiac catheterization and angiocardiography.

*Group 1—Accuracy of preoperative diagnosis established by clinical means only.* Eighty five (80 per cent) of the 106 clinical diagnoses were found at operation to be

*Table I. Cases found at operation to have a completely accurate preoperative diagnosis*

| *Preoperative diagnosis* | *Cases having correct diagnosis* | | |
|---|---|---|---|
| | *Group 1* | *Group 2* | *Group 3* |
| Tetralogy of Fallot | 18 | 4 | 2 |
| Ventricular septal defect | 13 | 5 | 2 |
| Coarctation of the aorta | 13 | | |
| Atrial septal defect | 12 | 13 | 2 |
| Patent ductus arteriosus | 10 | 3 | 1 |
| Aortic stenosis | 8 | 2 | 2 |
| Pulmonary stenosis | 3 | | |
| Atrioventricular canal | 2 | 3 | |
| Total anomalous pulmonary venous connection | 1 | 3 | 2 |
| Vascular ring | 1 | 1 | |
| Pulmonary stenosis and atrial septal defect | 1 | 1 | 1 |
| Transposition of great vessels | 1 | 1 | |
| Ventricular septal defect and coarctation of aorta | 1 | 2 | |
| Aortic stenosis and coarctation of aorta | 1 | 1 | 1 |
| Ventricular septal defect with mild pulmonary stenosis | | 3 | 1 |
| Ventricular septal defect and patent ductus arteriosus | | 3 | |
| Left-coronary-to-right atrium fistula | | 1 | |
| Atrial septal defect and patent ductus arteriosus | | 1 | 1 |
| Coarctation of aorta and patent ductus arteriosus | | 1 | |
| Tetralogy of Fallot and atrial septal defect | | 1 | |
| Tricuspid atresia | | 1 | 1 |
| Aortic stenosis and patent ductus arteriosus | | | 1 |
| Coarctation of aorta and hypoplastic right ventricle | | | 1 |
| Pulmonary stenosis and tricuspid insufficiency | | | 1 |
| Transposition of great vessels with ventricular septal defect and coarctation of aorta | | | 1 |
| Common atrioventricular canal, coarctation of aorta, patent ductus arteriosus and isolated levocardia | | | 1 |
| Aorticopulmonary window | | | 1 |
| Transposition of great vessels with ventricular septal defect and pulmonary stenosis | | | 1 |
| Tetralogy of Fallot with left pulmonary artery arising from patent ductus arteriosus | | | 1 |
| Coarctation of aorta, dextroposition of heart, ventricular septal defect, stenosis of left pulmonary artery, hypoplasia of right pulmonary artery, and stenosis of the right upper lobe artery | | | 1 |
| Total | 85 | 50 | 25 |

[illegible]

*Table II Additional unsuspected lesions found at operation*

| Preoperative diagnosis | Alteration in diagnosis made at operation | | |
|---|---|---|---|
| | *Group 1* | *Group 2* | *Group 3* |
| Tetralogy of Fallot | Agenesis of left pulmonary artery, persistent left superior vena cava, absence of inferior vena cava* | | |
| | Right pulmonary artery arising from ascending aorta | | |
| | Atrial septal defect† | | |
| | Atrial septal defect | | |
| | Atrial septal defect | | |
| | Tricuspid stenosis and atrial septal defect | | |
| Atrial septal defect | Mild mitral insufficiency | Mild mitral insufficiency | |
| | Mild tricuspid insufficiency | Anomalous pulmonary venous connection | |
| | Anomalous pulmonary venous connection | Anomalous pulmonary venous connection | |
| Ventricular septal defect | Partial atrioventricular canal | Patent ductus arteriosus | |
| | Mild mitral insufficiency | Mild pulmonary stenosis | |
| | Infundibular stenosis | Possible double outlet of right ventricle | |
| | Infundibular stenosis | | |
| | Infundibular stenosis | | |
| | Mild pulmonary stenosis | | |
| Pulmonary stenosis | Ventricular septal defect † | | |
| Patent ductus arteriosus | Ventricular septal defect | | |
| Coarctation of aorta, ventricular septal defect, and patent ductus arteriosus | Only coarctation of aorta | | |
| Coarctation of aorta alone | Patent ductus arteriosus | | |
| | Patent ductus arteriosus | | |
| Partial atrioventricular canal | Atrial septal defect of secundum type | Atrial septal defect of secundum type and anomalous drainage of coronary sinus | |
| Anomalous pulmonary venous connection and atrial septal defect | | No atrial septal defect. Grade 2 mitral insufficiency | |
| Double aortic arch | | Patent ductus arteriosus | |
| Ventricular septal defect, atrial septal defect, and pulmonary stenosis | | No ventricular septal defect | |
| Tetralogy of Fallot and atrial septal defect | | | No atrial septal defect |
| Ventricular septal defect and coarctation of aorta | | | Mild infundibular stenosis |
| Ventricular septal defect and mild pulmonary valve stenosis | | | Infundibular stenosis, not valvular |
| Ventricular septal defect and patent ductus arteriosus, possibly coarctation of aorta | | | Interruption of aortic arch |
| Ventricular septal defect, patent ductus arteriosus, possibly atrial septal defect | | | Tricuspid insufficiency |

*Course of operation [illegible]

†Catheterization was carried out in 3 cases [illegible] at that time

completely accurate The diagnoses in these 85 cases are listed in Table I

In 21 (20 per cent) of the 106 cases the clinical diagnosis was confirmed at operation but an additional clinically unsuspected lesion was also present In 17 cases the additional lesion did not materially alter the operation and accurate foreknowledge of its presence was not considered to be important In 4 cases the additional lesion was of major importance These lesions are listed in Table II

In no case was the clinical diagnosis completely erroneous

*Group 2—Accuracy of preoperative diagnosis suspected by clinical means but established by catheterization* The preoperative diagnosis suspected clinically but established by cardiac catheterization was found at operation to be completely accurate in 50 (83 per cent) of the 60 cases that comprised this second group These 50 cases are listed in Table I

In 10 of the 60 cases the preoperative diagnosis was correct but an additional unsuspected lesion was found at operation In 9 cases the presence of this additional lesion did not materially alter the operation but in 1 it resulted in an unnecessary ventriculotomy in that a ventricular septal defect had been diagnosed in addition to an atrial septal defect and mild pulmonary artery stenosis but in fact no ventricular septal defect was present

In none of these 60 cases was the diagnosis completely erroneous

*Group 3—Accuracy of preoperative diagnosis established only by cardiac catheterization* Of the 30 patients in this group 25 (83 per cent) were found at operation to have lesions exactly as predicted in the preoperative diagnosis These 25 cases are listed in Table I

In the other 5 cases the preoperative diagnosis was not completely accurate Four patients had an additional lesion that did not materially alter the course of treatment and 1 had an additional lesion that changed considerably the course of the operation In no case was the diagnosis completely erroneous

**Comment**

In the material reviewed a completely accurate preoperative diagnosis was made in about 80 per cent of cases Although the average complexity of the conditions to be diagnosed increased from Group 1 through Group 3 the accuracy of diagnosis was similar regardless of whether the diagnosis was established by clinical means alone (Group 1) when this was considered to be adequate by the clinician by a combination of clinical means and catheterization (Group 2) when this was deemed to be advisable or by cardiac catheterization predominantly (Group 3) when a secure clinical diagnosis could not be made Similar figures were obtained in the 162 cases in which catheterization was performed before referral to this clinic

Of the 36 cases in which a lesion was found at operation in addition to lesions diagnosed in only 6 (17 per cent) (3 per cent of total) was the operative procedure considerably altered by the unsuspected finding The incidence of such significant lesions for Groups 1 2 and 3 was 3 8 1 7 and 3 3 per cent respectively The pertinent question is whether catheterization of each patient including those in Group 1 for whom a confident clinical diagnosis was made is justified in order to discover all or nearly all of the additional lesions present Alternatively could continual improvement in diagnostic acumen stimulated by review of diagnostic accuracy and pitfalls be relied on to achieve the same end? Indeed the keystone of correct diagnosis is the astute clinician Data obtained at cardiac catheterization cannot be relied on exclusively in establishing consistently accurate diagnoses The practice of performing cardiac catheterization on a routine basis for patients with congenital heart disease might tend to dull the acuity of the clinician

This review indicates that the routine use of cardiac catheterization is not required for diagnostic purposes in all cases of congenital heart disease and that the additional expense discomfort and risk associated with this procedure should be reserved for selected cases of increased complexity or atypical nature It should be obvious that a major function of studies by catheterization lies in clear definition of those cases unsuitable for cardiac surgery at the present time and that an assessment of this negative value of

such diagnostic studies is not defined by this report

## Summary

Since successful cardiac surgery depends to some degree on a correct preoperative diagnosis a comparison was made of diagnoses based on clinical findings with those based on cardiac catheterization with respect to surgical diagnosis The records of 196 patients operated on for congenital heart disease from July 1963 through June 1964 were reviewed for this purpose A completely accurate diagnosis was made in about 80 per cent of the cases whether the diagnosis was made by clinical means alone by a combination of clinical means and catheterization or by catheterization alone The use of cardiac catheterization was decided upon on the basis of certainty of clinical diagnosis Of the cases in which unsuspected lesions were found at operation the operative procedure was considerably altered by the unsuspected findings in only 6 cases (3 per cent of the total) It is suggested that routine cardiac catheterization in all cases of congenital heart disease is not required

# The Polarcardiograph. Further studies of normal subjects, refinement of criteria for infarction, and a report on autopsied cases

*Gordon E. Dower, M.B.**
*Heidi E. Horn*
*Vancouver, Canada*

The usefulness of five simple criteria for the polarcardiographic diagnosis of myocardial infarction has been reported previously.[1] The evaluation was carried out on 493 patients, of whom 227 were considered, on the basis of electrocardiographic or postmortem evidence, to have suffered infarction. In these, the criteria gave the diagnosis in 94.7 per cent. On the other hand, two independent readers, using conventional electrocardiographic criteria, reached the diagnosis from the single electrocardiogram (ECG) recorded when the polarcardiogram (PCG) was taken in only 66.1 per cent. In 11.6 per cent of the total population, the PCG criteria indicated infarctions which could not be confirmed by available evidence. This figure provided an upper bound for the incidence of false positive diagnoses. A lower bound could not then be obtained because it would have required postmortem examination of all cases of false positive diagnoses.

A false-positive diagnosis is probably more serious in a younger patient. An acceptable upper bound for the incidence of false positives would be 5 per cent.[2] It was decided, therefore, to study a group of normal young adults, males and females, and to adjust the criteria to yield a false-positive rate of less than 5 per cent. This paper describes the results of such a study, the modifications in the criteria that were required, and their effect on the incidence of correctly diagnosed cases when reapplied to the previous group. Their application to a subgroup of 78 autopsied cases is also described.

## Method

*Selection of cases.* The definition of *normal* in a study of this type poses certain problems. It is not sufficient to take as normal those who have normal ECGs, because we are trying to appraise a more sensitive test—cases of infarction correctly diagnosed on PCG evidence might be treated as normal cases on the basis of the ECGs. Similar objections can be raised with respect to any medical examination that is carried out in an attempt to define normality. Therefore, it was decided to avoid a selection based on medical evidence. Since any hospital population tends to be selected on medical grounds, volunteers were obtained from a population found on the University campus.

Approximately 200 volunteers were stud-

From the [illegible] Hospital, and the Department of Pharmacology, University of British Columbia, Vancouver, British Columbia, Canada.
[illegible] British Columbia [illegible] Foundation.
Received for publication Dec. 31, 1965.
*Address: Department of Pharmacology, University of British Columbia, Vancouver, B.C., Canada.

ed. Because of obvious restraints on applying coercion to randomly selected individuals, the possibility that the act of volunteering produced some degree of selection must be accepted.

*Technical detail.* The transistorized version of the Polarcardiograph was used.[3] The x, y, and z orthogonal signals were obtained from Frank's lead system.[4] Subjects were studied in the supine position, so the chest electrodes were applied at the level of the fourth intercostal space.[4] As in previous studies, the position of the C electrode was located with a chest protractor. Buffer amplifiers were employed between the patient and the lead system network in order to avoid errors arising from unequal skin-electrode resistances. The x, y, and z signals were recorded separately on 3 of the 4 channels of an FM tape recorder. PCG and vectorcardiographic (VCG) readouts were derived from these recorded signals.

Recording the x, y, and z signals on magnetic tape allowed an innovation in clamping procedure.[4] The signals were reproduced at slow speed in reverse direction and observed on an oscilloscope. A clamp-triggering signal was injected onto the fourth channel of the tape recorder so that it fell during the P-R interval. This signal was then used to activate the clamping circuits of the Polarcardiograph during the final readout. Vectorcardiograms (VCGs) were obtained by means of a storage oscilloscope in which horizontal as well as vertical beam splitting was employed. This made it possible to display and photograph transverse, frontal, and sagittal loops simultaneously.

**Results**

The terminology used in this paper is that described previously.[4]

The tracings of 3 of the 198 volunteers from a university population were rejected because of technical imperfections. There were 3 cases with abnormal ECGs, but these were retained because of the requirement that medical grounds should not affect selection (*vide supra*). The age and sex distributions of the sample are shown in Table I.

*Table I. Age distribution of sample studied*

| Age (yr.) | *Males* | *Females* |
|---|---|---|
| 18–25 | 75 | 57 |
| 26–30 | 26 | 8 |
| 31–40 | 15 | 8 |
| 41 and older | 5 | 1 |
| Total | 121 | 74 |

*Normal values.* The frequency distributions and upper and lower 2½ percentiles encompassing 95 per cent of the sample of 195 young adults are compared with corresponding distributions and percentiles derived from 192 males whose mean age was 58.6 years and who were selected on the basis of normal ECGs. Percentile points were calculated according to the method of Simonson.[5]

QRS DURATION. Unlike an ECG, in which part of the QRS complex may be isoelectric in a given lead, the spatial magnitude curve of the PCG clearly indicates when all heart vectors are simultaneously zero and therefore provides a much clearer indication of the beginning and end of QRS. Furthermore, the paper speed used to record PCGs in the present study was 8 times faster than that generally used for ECGs, i.e., 20 cm per second.

The frequency distribution of the durations of spatial magnitude QRS complexes in the 195 young adults studied is shown in Fig. 1. Note that the distribution for females is slightly to the left of that for the total sample of young adults and corresponds with that for the 192 elderly men. The lower and upper percentiles for young adults are 64 and 108 msec., compared with 61 and 105 msec. for the elderly men (Table II).

P-R INTERVAL. The spatial magnitude curve of the PCG provides a convenient and accurate means of measuring this interval for reasons similar to those given above for QRS duration.

The frequency distributions and percentiles are given for the 195 young adults in Fig. 2 and Table II, respectively. There appears to be no sex difference in the distribution. Note that there were 5 cases

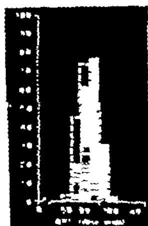


Fig. 1 QRS interval determined from spatial magnitude tracings of 195 young adults; females are shown by hatching. Previously reported intervals for 19 elderly men with normal electrocardiogram are shown by the dashed line



Fig. 2 P R interval in 195 young adults; females are shown by hatching

i.e. 2½ per cent with P R > 200 msec, one of these had a P R interval of 270 msec

SPATIAL MAGNITUDE OF MAXIMUM QRS AND T VECTORS AND THE RATIO BETWEEN THEM The maximum QRS vector R and the maximum T vector T have spatial magnitudes MR and MT whose frequency distributions for the 195 young adults are shown in Figs 3 and 4 and the ratio MT MR in Fig 5 There appears to be no marked sex difference in the MR distribution In the distributions for females males and the 192 elderly males there is a secondary peak to the right of the main peak A similar observation seems to be valid for MT which in addition shows a slight sex difference The distribution for females corresponds with that seen in the elderly males and lies slightly to the left of that seen for the young males The lower and upper percentiles for the mixed population are somewhat above those obtained for the 192 elderly men (Table II) The same comment applies to the percentiles of the ratio MT MR (Table II) which has the frequency distribution shown in Fig in which no marked sex or age difference is apparent

SPATIAL ANGLE BETWEEN MAXIMUM QRS AND T VECTORS The angle between R and T has the distribution shown in Fig 6 There is a slight sex difference the distribution for males lying slightly to the right The distribution covers a wide range the lower and upper percentile points are situated at

*Table II Comparison of 2½ percentile points in two normal studies*

| | 19 Elderly men with normal ECG | | 195 Young men and women ... | |
|---|---|---|---|---|
| | Lower | Upper | Lower | Upper |
| P R interval (msec ) | — | — | 11 | [illegible] |
| QRS duration (msec ) | 61 | 105 | 64 | 1 [illegible] |
| MR† (mv ) | 0 69 | 2 03 | 0 85 | [illegible] |
| MT (mv ) | 0 19 | 0 4 | 0 2 | 0 56 |
| MT/MR | 0 14 | 0 60 | 0 18 | 0 69 |
| R T angle (degrees) | 15 2 | 142 6 | 1 | 10 6 |

* ... 144
† Spatial magnitude of maximum QRS vector
‡ Spatial magnitude of maximum T vector

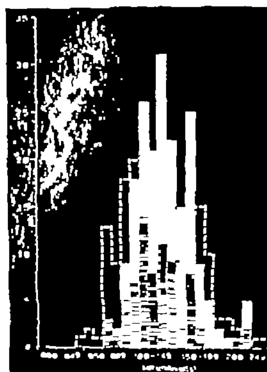


Fig. 3. Magnitudes of maximum QRS vectors in same samples as in Fig. 1.

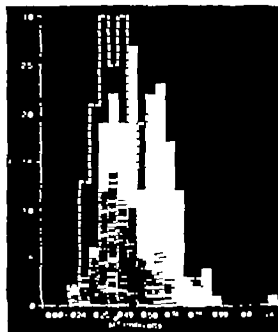


Fig. 4. Magnitudes of maximum T vectors in same samples as in Fig. 1.



Fig. 5. Ratio of magnitudes of maximum T to magnitudes of maximum R vectors in same samples as in Fig. 1.

15.7° and 110.6° (Table II); however, a definite difference can be seen between the distribution for the 195 young adults and the 192 elderly males. The latter shows a secondary peak well to the right of the main distribution, raising the upper 2½ percentile to 149.6° (Table II). This secondary peak probably indicates the inclusion of abnormal cases in the series. The angle between R̂ and T̂ is poorly indicated by the ECG, so that abnormalities in this variable may be consistent with normal appearing ECGs.

DIRECTIONS OF QRS AND T VECTORS. The directions of R̂ in the 195 young adults are shown in Fig. 7. The distribution for the females is roughly concentric with that for the males but is less scattered. In a generalization for both sexes, the distribution lies between latitudes 50I and 30A and between longitudes +10α and +90α, with a few exceptions exceeding +90α and lying posterior to 30I. For the corresponding distribution found for 184 elderly males, the reader is referred to the original article.[1] That distribution was roughly similar; it was centered over the +30α meridian



Fig 6 Angle between maximum QRS and maximum T vectors in same samples as in Fig 1

rather than the +50a meridian for the present series (Fig 7) However it showed more scatter there were 38 cases posterior to 50P as compared with 3 in Fig 7 All but 10 cases 95 per cent lie in an area one twelfth that of the globe

In some cases R̂ is ambiguous because of two peaks of equal height in the spatial magnitude tracing For this reason the vector IR has been proposed It is defined as the vector occurring at the instant at which the area beneath the QRS complex in the spatial magnitude tracing is half of its final value This is readily obtained from the simultaneously recorded integral of the spatial magnitude tracing The directions of IR are shown in Fig 8 The distribution is very similar to that for R̂ This suggests that the direction of IR may be substituted for that of R̂ when the latter is ambiguous Note that even though R̂ may be ambiguous MR the magnitude of R̂ is not hence it is not necessary to substitute the magnitude of IR for MR

The directions of T̂ in the 195 young adults are shown in Fig 9 The center of the distribution for females is about 20 degrees posterior to the center of the distribution for males but there is considerable overlap between the two distri

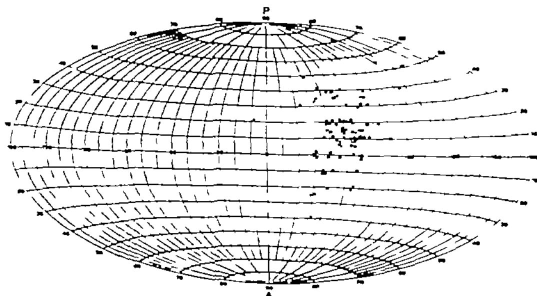



Fig 7 Directions of R in 195 young adults stars indicate females

butions The distribution for both sexes shows much less scatter than that noted for $\bar{R}$ and all but 6 cases 97 per cent lie in an area one nineteenth that of the sphere With 3 exceptions the distribution is bounded by longitudes $+10\alpha$ and $+60\alpha$ and latitudes 10A and 65A The case with the T direction on the 180 degree meridian close to the anterior pole had an abnormal ECG The distribution of $\bar{T}$ found for the 192 elderly males was approximately concentric with the above mentioned distribution but showed more scatter 95 per cent were contained in one fifteenth of the global surface[3] Thus the scatter for the young adults for T directions is 0 8 of that for the elderly men

## Criteria for infarction

*Application of criteria to 195 young adults—refinements* The PCC criteria for infarction previously reported are given in Fig 10[1] When these criteria were applied to the 195 young adults it was found that downslopes occurring early in the transverse and sagittal longitude tracings of the QRS vectors ($\beta_{QRS}$ and $\gamma_{QRS}$) were common However at the end of the initial $\beta_{QRS}$ downslopes it was noted that $\beta_{QRS}$ exceeded $+75$ in all but 9 cases Initial $\gamma_{QRS}$ downslopes occurred within the first 8 msec after the onset of the QRS complex in the spatial magnitude curve ($M_{QRS}$) in all but 7 cases These findings suggested refining the criteria as indicated in the right hand column of Fig 10 The refinement that a Q wave should appear in the y lead as a necessary condition for the diagnosis of inferior infarction is actually a consequence of the previous definition and not therefore a new condition however it is sometimes easier to apply in practice than $\gamma_{QR} > -175$ Note that the Q wave may be of any size If it is so small as to be equivocal the diagnosis would be doubtful or negative for inferior infarction Fig 11 illustrates $\beta_{QRS}$ and $\gamma_{QRS}$ downslopes which would not yield diagnoses of infarctions because of the above mentioned refinements

Application of the refined criteria to the 195 young adults gave the following result positives 6 (3 08 per cent) and doubtfuls 4 (2 05 per cent)

*Application of refined criteria to 493 cases previously reported*[1] The results of applying the refined criteria for infarction to the series of 493 cases previously studied are

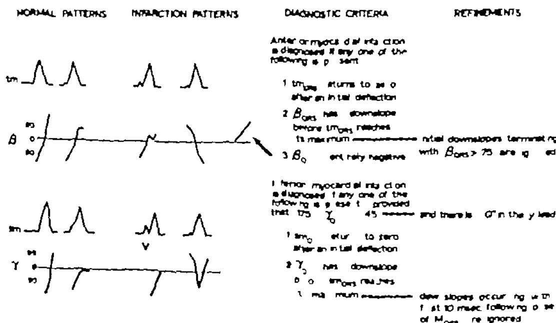



Fig 10 The polarcardiographic criteria for infarction with refinement

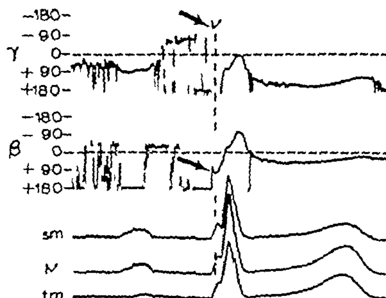



Fig. 11. The effect of the refinements in Fig. 10 negates a diagnosis of AMI: initial downslope terminates with $\beta_{QRS} > +75$ and of IMI: γQRS has a downslope which falls within first 10 msec. (*indicated by vertical dashed line*) after onset of $M_{QRS}$.

shown in Tables III, IV, and V. The figures in parentheses were obtained using the original criteria. Additional evidence, generally postmortem, has been acquired and applied to the current figures. One ECG diagnosis (ECGΔ) previously treated as doubtful should have been negative. This has been corrected. In the tables the PCGΔ is the diagnosis obtained employing the refined criteria. The ECGΔ is a composite based on the independent diagnoses of two skilled interpreters who saw separately the ECG taken at the time the PCG was recorded but who were given no other information. The BestΔ was based on all ECG and autopsy evidence available in those cases in which there was a conflict between the ECGΔ and the PCGΔ. In the absence of significant information or when they did not conflict, the PCGΔ and the BestΔ were the same.

In the 493 cases the PCGΔ was positive for infarction on the basis of the refined criteria in 269, negative in 217, and ambiguous in 7. The ambiguities derived from very small abnormalities associated with muscle tremor. Of the 269 cases in which the PCGΔ was positive, the ECGΔ was positive in only 143, but when more information was provided about many of these cases, agreement with the PCGΔ improved: the BestΔ was positive for 206 cases. Thus there was a trend toward the PCGΔ of 63 cases. When the PCGΔ was negative, there were only 6 cases in which the ECGΔ was positive. No distinction between subendo

*Table* III. *Diagnosis of myocardial infarction (out of 493 cases). Polarcardiographic diagnosis (PCGΔ) vs. diagnosis from single ECG (ECGΔ) and from all ECGs and postmortem data (BestΔ) (where relevant)*

| | PCGΔ+ | PCGΔ− | PCGΔ? |
|---|---|---|---|
| ECGΔ+ | 143 (146) | 6 (3) | 1 (1) |
| − | 5 (93) | 194 (173) | 4 (7) |
| ? | 51 (56) | 17 (14) | 2 (1) |
| | 269 (291) | 217 (190) | 7 (9) |
| BESTΔ+ | 206 (215) | 25 (10) | 3 (2) |
| − | 44 (57) | 185 (174) | 4 (7) |
| ? | 19 (22) | (6) | 0 (0) |
| | 269 (291) | 21 (190) | 7 (9) |

Figures in parentheses are those previously reported, employing the original criteria.

*Table IV Result of combining + and − diagnoses for myocardial infarction in PCGΔ ECGΔ and BestΔ out of 493 cases*

| *PCGΔ agreement (as to occurrence or non occurrence of infarction)* | *With ECGΔ (cases)* | *With BestΔ (cases)* |
|---|---|---|
| Complete as to location of infarction | 96 (93) | 144 (162) |
| Not complete as to location | 45 (53) | 58 (53) |
| As to occurrence of infarction | 141 (146) | 202 (215) |
| As to nonoccurrence of infarction | 190 (173) | 182 (174) |
| Total agreement | 331 (319)<br>67 2% (64 7%) | 384 (389)<br>78 0% (78 9%) |

Figures in parentheses those previously reported employing original criteria

*Table V Incidence of false positives in PCGΔ based on various yardsticks*

| | *In series of 493 cases* | | *In 78 autopsies* | *In 19[illegible] young adults* |
|---|---|---|---|---|
| | *Based on ECGΔ* | *Based on BestΔ* | *Based on P M findings* | *Based on assumptions of normality* |
| Incidence of false positives in PCGΔ (per cent) | 14 6 | 8 5 | 6 4 | 3 1 |

cardial and transmural infarction is made in Table III there were 21 cases in which the ECGΔ was subendocardial infarction i e the diagnosis was not based on the QRS complex Although the PCG criteria so far relate only to the QRS complex the diagnosis of *infarction was made in 16* of these cases There were only 7 cases in which the PCGΔ was doubtful whereas there were 70 cases in which the ECGΔ was doubtful—a figure which was reduced to 76 in the BestΔ Comparison with the earlier figures shows that there are now only 9 fewer cases with both the BestΔ and the PCGΔ positive Additional information has added 7 cases to the total number with the BestΔ positive

In some cases a diagnosis of both anterior infarction (AMI) and inferior infarction (IMI) was made on the basis of the refined ECG criteria whereas the ECGΔ or the BestΔ indicated either one of these and vice versa Agreement as to location was considered to be partial in these cases There was complete agreement as to location of the infarct in 96 cases with the ECGΔ and in 144 cases with the BestΔ (Table IV) The PCGΔ differed as to *location of the infarct* from the ECGΔ in 45 and from the BestΔ in 58 cases Agreement as to whether or not infarction had occurred existed in 331 cases (67 2 per cent) with the ECGΔ and in 384 cases (78 0 per cent) with the BestΔ These figures are not greatly different from those previously obtained with the unrefined criteria (Table IV in parentheses)

As already indicated the object in refining the criteria for infarction was to guard against an excessive number of false positives especially in young adults In the 493 cases the incidence of apparent false positives based on various yardsticks is shown in Table V On the basis of the

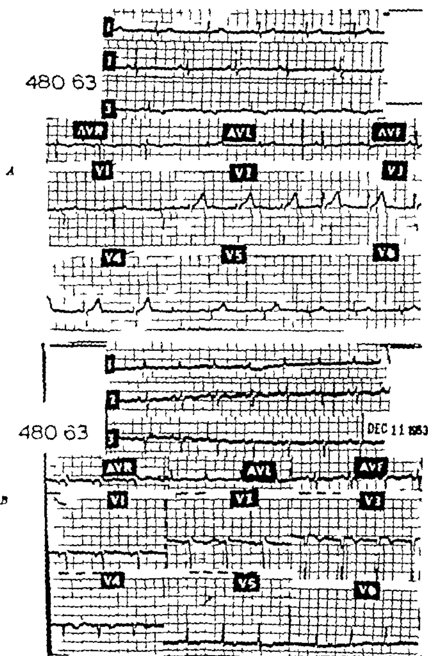



Fig. 17. Changes secondary to subacute bacterial endocarditis. A, Six months before death. B, One month before death.

ECG A it is 14.6 per cent, but when more information is provided, as in the Best A, it reduces to 8.5 per cent. This would still be too high were it not for the expectation that further information would reduce it.

In summary, in the group of 493 cases on the basis of all ECG and EM evidence available, the diagnosis of infarction was made in 234 cases. In these cases the diagnosis based on the ECG alone was infarction in 150, or 64 per cent. In the same cases, the diagnosis based on the ECG alone, employing the refined criteria, was infarction in 206, or 85 per cent.

*Application of refined criteria to 75 autopsied cases.* Out of the 493 cases referred

to above autopsies were obtained in 78 and the hearts in 61 were examined by at least one of the authors The importance of being present when autopsy examination of the heart is carried out should be stressed This does not imply criticism of the pathologists but merely the fact that one tends to discover something more readily if one is looking for it All too frequently the postmortem report supported by a cursory pathologic examination is erroneously considered to be the final verdict [4]

Of the 78 autopsied cases infarcts were found at autopsy in 58 The ECGΔ was positive in only 23 or 40 per cent of these whereas the PCGΔ was positive in 46 or 79 per cent

There were 6 cases in which the PCGΔ was positive but no infarcts were found at autopsy It is most unfortunate that the hearts in 4 of these cases were not available to the authors and were not bread loafed [7] Death in 1 of these cases was due to subacute bacterial endocarditis and autopsy showed multiple small areas of myocardial fiber replacement by granulation tissue Before death ECGs showed typical changes of infarction (Fig 12) From an electrical standpoint the lesions seen were equivalent to infarcts so that this case should not fairly be considered to be a false positive Thus there were 5 false positives for the PCGΔ or 6 4 per cent (Table V) However in one of these the previous ECGs were strongly suggestive of anterior infarction the patient had had typical attacks of angina and had been considered to have a typical infarction on clinical grounds The heart weighed 550 grams it was not bread loafed and it may be that a significant infarction was missed at autopsy in this case If true the false positive rate was 5 1 per cent

**Discussion**

The normal study reported here is of interest not only because it furnishes a definition of normal that is statistically acceptable but also because it provides a basis for comparison between samples of almost equal size from two different populations—a mixed population of young presumably healthy adults and a population of elderly males who had normal ECGs The rather small differences between the percentile PCG data and angular plots obtained from the two samples despite a rather wide discrepancy in age suggests that the variables studied tend to be rather stable with age This is satisfactory because it means that age factors may not need to be taken into account in PCG interpretations applied to adult populations Furthermore although a slight sex difference was noted in some distributions in the present series the difference would probably be small enough to be neglected for most purposes The fact that different instruments were used in the two studies and that these employed radically different components and had different readouts calibration procedures and paper speeds yet gave results that were remarkably close speaks well for the accuracy of the technique

Distributions for QRS and T latitudes and longitudes employing a longitudinal polar axis for 175 normal men have been reported recently by Beswick Jordan and Kilpatrick [8] However the directions they gave were obtained by employing the areas of the QRS complex and the T wave in the x y and z orthogonal leads as x y and z coordinates to define QRS and T vectors respectively These vectors do not correspond with R̂ and T̂

As stated in the introduction the reason for this normal study was to ensure that the incidence of false positives was not excessively high Table V presents various estimates of this incidence In the 493 cases if the ECGΔ is taken as a yard stick the incidence of false positives is 14 6 per cent If this figure were very much lower there would be little to be gained from the use of the PCG because it would indicate that if the PCGΔ was positive then the ECGΔ would be positive too When all the ECG and autopsy evidence available is taken into consideration the false positive rate falls to 8 per cent However the evidence in this series of 493 cases is not complete and it might well be that more evidence would reduce this rate further In the 78 autopsies in which the evidence was complete the rate fell to 6 4 per cent for the 195 young adults the rate was 3 1 per cent

The modified diagnostic criteria fo

myocardial infarction may thus be employed with confidence that the odds against any given positive PCG being wrong are 20:1.

**Summary**

A population sample of 195 young men and women has been studied in order to define normal values for polarcardiographic diagnosis and to refine five simple criteria for infarction to yield an incidence of false positives of less than per cent. The incidence became: positives 3 per cent, doubtfuls 2 per cent. The criteria were reapplied to a group of 493 patients who had been studied previously and to 78 autopsied cases which formed a subgroup. In the 493 patients there were 234 who were considered to have suffered infarction. In these the refined criteria gave the diagnosis in 88 per cent. On the other hand, two independent readers using conventional criteria reached the diagnosis from the single ECG recorded at the same time as the PCG in only 64 per cent. In the 78 autopsied cases there were 58 with infarcts. The ECG gave the diagnosis in 40 per cent of these whereas the ECG gave the diagnosis in 9 per cent.

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# A simplified method for calculating the pulmonary valvular area

*James H. Moller, M.D.*
*Paul Adams, Jr., M.D.*
*Minneapolis, Minn.*

The selection of patients with isolated pulmonary valvular stenosis for operation is commonly made on the basis of the level of right ventricular systolic pressure. The severity of the pulmonary stenosis can be more accurately assessed when both the right ventricular pressure and the cardiac output are considered. In 1951 Gorlin and co-workers[1,2] presented formulae for pulmonary valvular area and pulmonary valvular resistance. These formulae consider various relationships between the right ventricular pressure and the cardiac output.

The determination of the pulmonary valvular area yields information which is easily understood by the clinician and surgeon evaluating a patient with pulmonary stenosis. The formula for pulmonary valvular area is probably not more widely applied because of several time-consuming steps necessary in performing the calculation from the pressure tracings recorded at catheterization.

The purpose of this communication is to present a simplified method of determining the pulmonary valvular area which eliminates the necessity of measuring various factors of the pressure contour. This method is based on data obtained at cardiac catheterization in children with isolated pulmonary valvular stenosis and by the application of the formulae of Gorlin[1] to the analysis of this data.

## Source of data

In 108 children with isolated pulmonary valvular stenosis studied in the cardiovascular laboratory at the University of Minnesota Hospitals, pressure tracings recorded at cardiac catheterization were adequate for this analysis. In 40 of the 108 cases, oxygen consumption was determined by the Tissot-Scholander method, so that by applying the Fick principle the cardiac output could be calculated, utilizing the simultaneously measured arteriovenous difference in oxygen content.

Pulmonary valvular area and the pulmonary valvular resistance were calculated in each of these 40 cases utilizing the following formulae of Gorlin[1,2]:

$$PVA\ (cm^2) = \frac{\text{systolic flow}}{\text{velocity through valve}}$$

$$PVA = \frac{\dfrac{CO \times 1{,}000}{SEP \times HR}}{44.5\sqrt{RV_m - PA_m}}$$

$$PVR\ (\text{dynes sec cm}^{-5}) = \frac{\text{pressure gradient}}{\text{flow}}$$

$$PVR = \frac{RV_m - PA_m}{CO} \times \frac{1{,}332 \times 60}{1{,}000}$$

From the Department of Pediatrics, University of Minnesota, Minneapolis, Minn.

This study was supported by Public Health Service [illegible] HE-1[illegible] and Research [illegible] HE-5694 from the National Heart Institute and the [illegible] Family Fund.
Received for publication [illegible]

PVA = pulmonary valvular area PVR = pulmonary valvular resistance CO = cardiac output $RV_m$ = mean right ventricular systolic ejection pressure $PA_m$ = mean pulmonary arterial pressure SEP = systolic ejection period and HR = heart rate

To determine the mean right ventricular systolic ejection pressure the right ventricular pressure contour was analyzed and perpendiculars were dropped to the zero line of the recording from the point in systole at which the right ventricular pressure first exceeded the pulmonary arterial pressure and from the dicrotic notch The interval between these two perpendiculars is the systolic ejection period i e the period when the pulmonary valve is open The area under the right ventricular pressure curve between the perpendiculars was measured by a planimeter and divided by the distance between the perpendiculars to find the mean right ventricular systolic ejection pressure In each instance duplicate or triplicate measurements were made of each of four ventricular complexes

The mean pulmonary arterial pressure was used instead of the mean pulmonary arterial systolic ejection pressure This assumption introduced only a small error in the calculations since the values are nearly identical

**Observations**

Of the formulae for pulmonary valvular area and for pulmonary valvular resistance the latter requires the least number of steps in its calculation If a constant relationship existed between these formulae by calculating the pulmonary valvular resistance one could determine pulmonary valvular area In the formula for pulmonary valvular resistance however the value for the mean right ventricular systolic ejection pressure is required in the calculation

Our initial step was to determine whether a direct relationship existed between the right ventricular systolic pressure and the mean right ventricular systolic ejection pressure In 108 cases the values for the right ventricular systolic pressure measured at the time of catheterization were compared to the values of the mean right ventricular systolic ejection pressure de-

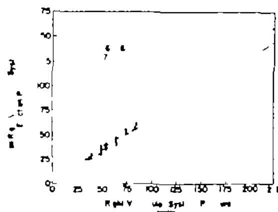


Fig 1 Relationship between right ventricular systolic pressure and mean right ventricular systolic ejection pressure in 108 children

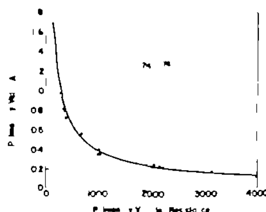


Fig 2 Relationship between pulmonary valvular area (cm ) and pulmonary valvular resistance (dynes sec -cm ) in 40 children with measured cardiac output

termined by the method outlined above There is a linear relationship between these two measurements of pressure (Fig 1) The mean right ventricular systolic ejection pressure is equal to 0 66 peak right ventricular systolic pressure ($y = 3.16 + .63x$ $r = .97$) This ratio of 0 66 is similar to that found by other workers Since a linear relationship exists between these two factors one can estimate the mean right ventricular systolic ejection pressure by knowing the peak right ventricular systolic pressure The necessity of making measurements from the right ventricular pressure contours is thereby eliminated and this factor may be used to calculate the pulmonary valvular resistance

In Fig 2 the pulmonary valvular area calculated by Gorlin's method has been related to the pulmonary valvular resistance in the 40 patients in whom the cardiac output was measured The values are clustered along the curve ($y = 74e^{[illegible]}$) By knowing the pulmonary valvular resistance therefore one can estimate a corresponding pulmonary valvular area

**Conclusions**

To determine the pulmonary valvular area the formula for pulmonary valvular resistance is utilized

$$PVR = \frac{RV_m - PA_m}{CO} \times \frac{1.332 \times 60}{1\,000}$$

A substitution of 0 66 peak right ventricular systolic pressure is made for the mean right ventricular systolic ejection pressure and the pulmonary valvular resistance is calculated

$$PVR = \frac{0.66\,RV - PA}{CO} \times 80$$

This value for resistance is located on the abscissa of Fig 2 and the corresponding pulmonary valvular area is found on the ordinate

**Summary**

In order to accurately assess the severity of pulmonary valvular stenosis one must consider both the right ventricular systolic pressure and the cardiac output The calculation for the pulmonary valvular area utilizes both of these factors but has been time consuming to perform A simplified method is presented for determining the pulmonary valvular area by calculating the pulmonary valvular resistance and relating this value to the pulmonary valvular area

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# Ectopia lentis, cardiology, and "the sign of the tremulous iris"

*John H. Stone, M.D.**
*Atlanta, Ga.*

Ectopia lentis, or displacement of the lens of the eye, is a finding that in many ways is as important to the cardiologist as to the ophthalmologist. The purpose of this communication is summarized as follows: (1) to review the pertinent pathologic anatomy, (2) to outline the disease entities in which displacement of the lens occurs, and (3) to underscore a physical finding which is familiar to the ophthalmologist but which, I believe, is often not utilized fully by the internist or cardiologist.

### Pathologic anatomy

If the suspensory ligaments which fix the lens in place are defective (see Fig. 1), the lens loses some of its support and may assume any of a number of positions. If rupture of the ligaments is not extensive, the lens remains in the pupillary aperture and is said to be *subluxated*. When subluxation alone is present, a number of optical events ensue. Because the lens is displaced from the center of the pupil, light is bent through the more highly refractile periphery of the lens and a lenticular myopia is usually produced.[1] The patient himself may note diplopia, since part of the light passing through the pupil is refracted by the subluxated lens and part is not; thus two images are formed on the retina. Astigmatism may occur if the lens is tilted on its axis.

If the ligaments are extensively ruptured, the lens moves out of the pupillary opening and is said to be *dislocated*. Under those circumstances, it may move into either the anterior chamber or posteriorly into the vitreous (in the latter case coming to lie finally against the retina). Secondary glaucoma is very likely to occur with displacement anteriorly. Posterior displacement is better tolerated, but complications, including glaucoma, usually ensue eventually.[1]

### Associated diseases

Ectopia lentis has been noted in several disease entities, including some of those designated as "heritable disorders of connective tissue."[2] These and other processes (see Table I) will now be reviewed.

Of the disease processes in which ectopia lentis is present, Marfan's syndrome stands foremost. Indeed, this ocular finding is one of the salient characteristics of this disorder. Other major signs may be found in the skeletal and cardiovascular systems. Arachnodactyly, kyphoscoliosis, pectus deformities, and hyperextensible joints are frequent skeletal abnormalities. Cardiovascular pathology is an important cause of death and includes aortic or pulmonary artery aneurysmal dilatation and/or dissection, sacculation of the aortic cusps,[3] and mitral insufficiency.[4] Congenital heart lesions have also been seen with Marfan's syndrome, but their relationship to the primary connective tissue disorder is un

Received for publication Jan. 4, 1966.
*Address: State of Georgia Department of Public Health, 47 Trinity Ave., S.W., Atlanta, Ga. 30334.

*Table I Conditions in which ectopia lentis may occur*

1 Marfan syndrome
2 Homocystinuria
3 Brachydactyly (Weill Marchesani) syndrome
4 Ehlers Danlos syndrome
5 Osteogenesis imperfecta
6 Ocular trauma
7 Spontaneous

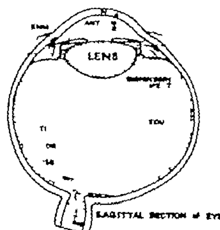



Fig 1 Normal anatomy of the eye

clear[3] McKusick[4] estimates that perhaps 70 per cent of patients with ectopia lentis will have stigmata of Marfan s syndrome conversely about 80 per cent of patients with Marfan s syndrome have ectopia lentis In this regard it is of interest that in his original case report of a man with long slender extremities and dolichocephaly Marfan stated specifically that the eyes were normal[4] The subluxation in this entity is usually superior and bilateral[5]

In 1963 a new inborn error of amino acid metabolism was recognized This syndrome called *homocystinuria* closely mimics Marfan s syndrome including ectopia lentis and similar skeletal abnormalities[7] Ectopia lentis has been found in the great majority if not all of patients with homocystinuria and as in Marfan s syndrome myopia retinal detachment and glaucoma may also occur Cardiovascular problems mainly arterial and venous thromboses are often present Aortic regurgitation seen frequently with Marfan s syndrome has not yet been observed in homocystinuria[8]

Ocular abnormalities including ectopia lentis spherophakia microphakia and glaucoma are major features of the brachydactyly or Weill Marchesani syndrome The other physical findings in this entity—short stubby fingers small stature and mental retardation—stand in sharp contrast to those in Marfan s syndrome[9] However one family which contained over thirty examples of Marfan s syndrome also had two members with features suggestive of the brachydactyly syndrome This led the author to suggest that the two disease processes may overlap or indeed be *genetically* the same[4] No specific cardiovascular findings have to my knowledge been described

Ectopia lentis has been noted at least once in both the Ehlers-Danlos syndrome[10] and osteogenesis imperfecta[11] as recorded by McKusick The Ehlers Danlos syndrome characterized by hyperelasticity of the skin and hyperextensibility of the joints is most significant to the cardiologist because of the occasional dissecting aneurysm In general though cardiovascular pathology is notably lacking A case of Ehlers-Danlos syndrome with a sinus of Valsalva aneurysm and aortic insufficiency has been reported[12] A recent report of a case with bifidity of the pulmonary artery and anomaly of the aortic arch (abnormal course of aorta and tortuous efferent vessels) has appeared[13]

Another recent paper[14] indicates that patients with osteogenesis imperfecta may also have significant associated heart disease Of the 3 patients whose cases were included in the above report two had aortic insufficiency secondary to dilatation of the aortic root without apparent cause the third patient had lesions of the pulmonary aortic and mitral valves and microscopic changes of cystic medionecrosis were present in the pulmonary artery and aorta

Dislocation of the lens occurs mo t fre*quently* on a traumatic basis It appears it may also occur spontaneously ... middle aged or older individual ... in cases in which the ...

### Examination for ectopia lentis

A complete ophthalmologic examination for ectopia lentis including use of the slit lamp may reveal minor but important changes in the suspensory ligaments. This sophisticated examination, however, although highly desirable in some cases, may not be necessary in many others if an informed physical examination is done. As can be appreciated from the accompanying figure, a subluxated lens may be seen with the ophthalmoscope, the curved edge of the lens appearing as a dark line in the pupillary aperture.[1] However, the pupil is almost always small and difficult to dilate (especially in Marfan's syndrome), and this may preclude or render ophthalmoscopic examination difficult at best.

### The tremulous iris

An even simpler diagnostic maneuver is used by ophthalmologists. Because the lens is subluxated, the anteriorly placed iris loses some of its support, and fluttering of the iris occurs.[4] As the patient moves his eyes from side to side, the iris is noted to tremble, either in part or as a whole. This sign is known as *iridodonesis*. That the ophthalmologist finds this a useful sign is attested to by the fact that Lutman and Neel[16] mention iridodonesis as a positive finding in the great majority of their cases of Marfan's syndrome. I have recently observed several patients with Marfan's syndrome who exhibited iridodonesis to a striking degree. Subsequent conversation with some of my medical colleagues concerning these patients prompted me to delve further into the subject and to write this report.

The only other major circumstance in which iridodonesis may occur is after cataract extraction, as would be expected from the foregoing discussion.

It is my impression that the clinical usefulness and *ease of application* of the sign of the tremulous iris has not been fully appreciated by cardiologists and internists, especially. Whereas some cases of ectopia lentis may not exhibit this sign, when it is present it appears to be a sure sign of subluxation of the lens.[1] As such it may prove to be useful in the continuing correlation of physical findings with the pathologic anatomy of disease.

Appreciation is expressed to Dr. Charles F. Cooper, Jr., Dr. J. Gordon Barrow, and Dr. J. Willis Hurst for their review of this manuscript. The illustration was done by Miss Pam Waddell, Medical Communications, Piedmont Hospital, Atlanta, Ga.

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# Myocardiopathy in Chagas' disease

## I Comparative study of pathologic findings in chronic human and experimental Chagas' myocarditis


*Alfonso Anselmi, M.D.**
*Felix Pifano C., M.D.**
*Jose Angel Suarez, M.D.***
*Orlando Gurdiel, M.D.*
*Caracas, Venezuela*


Great emphasis has been placed in the past on the importance of scattered fibrotic plaques found in heart musculature presenting chronic inflammation due to *Schizotrypanum cruzi* (*S. cruzi*).

Dias and associates[1] have stressed the presence of thinning of several regions in the free ventricular walls, and Laranja and associates[2] have found marked thinning of the left ventricular apex in 3 necropsy cases. These changes have been attributed by other authors[3-5] to confluent fibrotic processes predominating at the apex, producing at times aneurysm-like dilatations of the affected ventricular wall.[2,4-6]

Mora[4] was the first to describe thinning of the free ventricular wall and the formation of aneurysms in a case of Chagas' myocarditis at a site other than that classically described. Frequent discrepancies have arisen, also, in regard to the pathogenetic mechanism responsible for the degenerative changes observed in muscular fibers and replacement of them by collagen fibers. It has been suggested that the causative factors of the histologic changes produced by *S. cruzi* are mechanical destruction of fibers by the parasite,[9,12] toxic[3,13,14] or immunoallergic mechanisms,[6,15] [illegible] neurogenetic factors,[illegible] vascular factors,[illegible] and anoxia of the fibers due to hypertrophy of the interstitial space.[illegible]

In the present study an analysis is made of the pathologic findings in dogs with chronic experimental *S. cruzi* infection. These findings are compared with those in human autopsy material from the Institute of Pathology of the Universidad Central de Venezuela. Finally, an attempt is made to study the changes produced in the ventriculogram by the areas of fibrosis in experimental Chagas' myocarditis and in the anatomic-electrocardiographic correlations in human beings.

### Material and method

Twenty-nine hearts from patients showing a chronic inflammatory process at autopsy were studied histologically. The findings obtained were correlated with corre


[illegible] Received for publication [illegible] 1966.
[illegible] Caracas, Venezuela.
Address [illegible]: Dr. Alfonso Anselmi, Laboratorio [illegible] Caracas, Venezuela.

sponding electrocardiographic changes. The selection of cases was based on clinical and pathologic data. At this point, we should like to add that autopsies 1 to A 2503 were performed without following specific criteria. Although our impression is that there were some cases of chagasic myocardiopathy among them, the correct diagnosis was not confirmed except in Cases A 826, A 1217, A 1731, A 2199, and A 2503. Clinically, the cases selected for study were those which had a suggestive epidemiologic background, a positive complement fixation reaction (CFR) for *S. cruzi*, and clinical and electrocardiographic evidence compatible with that observed in chronic Chagas' myocarditis. From the pathologic point of view, the cases were selected on the basis of macroscopic flaccidity of the myocardium and dilatation of the chambers with or without mural thrombosis. Microscopically, all these cases had a focal or diffuse inflammatory reaction in the free ventricular and atrial walls of the heart and an absence of inflammatory reaction in other organs.

A correlation between pathologic and electrocardiographic findings was made in experimental animals. Techniques of infection in dogs, the evaluation of myocardial da[illegible] and the tracing methods employed h[illegible] described previously.[illegible] An absen[illegible] atherosclerotic coronary lesions wa[illegible]ed in all of the cases studied.

The preparation of the hearts was as follows: the heart was separated from the structures to which it was attached and was removed from the thoracic cavity. Care was taken to obtain sufficiently long pulmonary and caval veins. After initial washing, 10 per cent formalin was injected into the left and right chambers. The left chamber was injected via a pulmonary vein with ligatures placed on the other pulmonary vein and the aorta, and the right chamber was injected via a superior vena cava with previous ligation of the inferior vena cava and the pulmonary artery. Injection pressure was 50 ml. of water. The heart was then submerged in 10 per cent formalin for 5 days so that it would retain its natural shape and size.

Sections perpendicular to the longitudinal axis from apex to base were made at 5 mm. intervals. For histopathologic study, blocks were taken from the anterior, lateral, and posterior surfaces of the left ventricle and from the anterior and posterior surfaces and edge of the right ventricle. Superior, middle, and inferior areas of these were selected for sectioning. Blocks from the middle, superior, and apical areas of the interventricular septum were also taken.

Areas of intense and generalized fibrosis and their surroundings, and areas with thinning of the ventricular wall were included in those blocks in order to analyze the affected regions plus the ones around them. Sections were stained with hematoxylin-eosin, Gomori, and Van Gieson stains.

An important reduction in thickness was taken as the criterion of thinning of the free ventricular wall, together with normal thickness in the neighboring areas. In the right ventricle, with normally thin walls, the criterion for decreased thickness was translucency of a given area.

### Results

*I. Gross anatomy.* Hearts from patients with chronic myocardiopathy of chagasic origin present a macroscopic increase in total volume due to dilatation of the chambers. The degree of dilatation was significant and was present in all chambers in most of the cases studied. Table I shows the degree of dilatation on a scale of I to IV in each case. Only 3 cases (A 2769, A 3057, and A 3293) showed scant dilatation, but this was in conjunction with hearts of smaller size.

An important reduction in the thickness of the free ventricular wall was found in the majority of cases. Few hearts had walls of normal thickness, for the reason that hypertrophy of the heart was related to weight, which varied from 260 to 750 grams.

In experimental cases, chronic Chagas' infection (with a duration longer than 1 year and frequent reinfections) produces significant dilatation of all chambers, although the right ventricle is found to be affected more frequently. Fig. 8 shows the results of a 5 year infection in a dog: there is dilatation of all chambers, with a significant decrease in the thickness of the free left ventricular wall and thinning and fibrosis of the free right ventricular wall.

*Table I. Postmortem findings in 29 human cases*

| Autopsy number | Age (yr) | Sex | Dilatation LA | Dilatation RA | Dilatation LV | Dilatation RV | Dilatation RVOT | Thrombosis RA | Thrombosis LAAp | Thrombosis RAAp | Thrombosis LV | Thrombosis RV | Heart weight (Gm) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A 826 | 26 | F | III | IV | IV | IV | IV | | | + | + | + | 630 |
| A 1217 | 48 | M | II | III | III | IV | III | | | | + | | 685 |
| A 1781 | 31 | M | III | IV | IV | IV | III | | | + | + | + | 600 |
| A 2199 | 50 | F | II | III | III | III | III | | | + | + | | 520 |
| A 2503 | 66 | F | | I | I | II | I | | | | + | | 316 |
| A 2731 | 36 | F | II | II | III | II | I | | | | + | | 480 |
| A 2769 | 45 | F | | | I | I | | | | | | | 260 |
| A 2930 | 15 | F | I | I | III | II | III | | | + | + | | 453 |
| A 2952 | 64 | M | II | II | II | I | II | | | + | | | 498 |
| A 2954 | 44 | F | I | II | II | II | III | | | | | | 490 |
| A 2971 | 40 | M | II | III | II | III | III | | | + | + | + | 436 |
| A 2981 | 40 | M | III | III | IV | IV | IV | | | + | | + | 424 |
| A 2984 | 66 | M | II | III | III | II | III | + | | + | + | | 464 |
| A 3057 | 22 | F | | I | | I | II | | | | | | 275 |
| A 3093 | 64 | F | II | III | II | II | II | | + | + | | | 302 |
| A 3096 | 32 | M | II | II | II | III | III | | | + | + | | 414 |
| A 3116 | 18 | F | II | III | II | III | III | | | | | | 400 |
| A 3177 | 66 | F | II | III | II | II | III | | | | | + | 370 |
| A 3183 | 32 | F | III | III | III | III | III | | | | | | 665 |
| A 3185 | 38 | M | III | IV | IV | III | IV | | | + | | | 498 |
| A 3197 | 34 | M | | I | II | II | II | | | + | | | 438 |
| A 3199 | 64 | F | II | III | II | III | II | | | + | | | 370 |
| A 3247 | 54 | M | I | III | III | II | II | | | | | | 510 |
| A 3250 | 55 | F | I | II | II | II | II | | | + | + | + | 300 |
| A 3253 | 66 | M | II | III | III | III | III | | | | + | + | 537 |
| A 3286 | 33 | M | III | IV | IV | IV | IV | | | + | + | | 785 |
| A 3293 | 48 | M | | | | I | I | | | | + | | 290 |
| A 3320 | 55 | M | II | III | II | III | III | | | + | r | | 670 |
| A 3362 | 45 | M | III | III | II | III | III | | | + | | | 487 |

LA Left atrium RA Right atrium LV Left ventricle RV Right ventricle RVOT Right ventricular outflow tract LAAp Left atrial appendage RAAp Right atrial appendage

*Table II. Type and distribution of lesions in human cases (postmortem study)*

| | |
|---|---|
| Single lesion (3 cases) | 3 cases with fibrosis and thinning at LV apex |
| | 1 case with fibrosis and thinning at the superior aspect of the RV posterior wall |
| | 1 case with fibrosis and thinning at the superior aspect of the posterior wall of the LV |
| Multiple lesions | 6 cases LV apex—Posterior wall LV |
| | 1 case LV apex—Lateral wall LV (high) |
| | 1 case LV apex—Anterior and lateral wall LV |
| | 1 case LV apex—Anterior and lateral wall LV<br>Posterior wall RV |
| | 1 case LV apex—Posterior wall LV—Middle interventricular septum |
| | 1 case LV and RV apex—Anterior wall LV |
| | 2 cases LV and RV apex—Posterior wall LV |
| | 1 case LV and RV apex—Lateral and posterior wall of LV |
| | 1 case LV and RV apex—Posterior wall LV<br>Posteroinferior interventricular septum |
| | 1 case RA—Posterior and anterior walls RA |

Both the human and canine hearts showed significant muscular flaccidity the organs were easily depressed under pressure and showed creases when placed over a hard surface

Of the 29 human cases studied 21 presented the previously described anomalies 8 did not show thinning or extensive fibrosis in the cardiac walls Of the 21 pathologic cases 5 showed a single lesion (fibrosis and thinning of the right or left free ventricular wall) and 16 showed multiple lesions (fibrosis and thinning in several zones of the heart) The distribution of the anomalies is shown in Table II The lesions found were of an irregular round shape and they varied in size from 1 to 4 cm

Fig 1 (A 3183) shows the typical ventricular dilatation with thinning of the ventricular wall in the anterior and posterior regions The lateral wall shows a semicircular fibrotic zone extending from the anterolateral surface to the posterior surface and small foci of fibrous tissue in the subendocardium The translucent zone at the apex of the left ventricle is due to an extensive area of fibrosis which produced a foliaceous thinning at that level



Fig 1 Transverse section at the level of the inferior half of a heart (A 3183) with chronic myocarditis of 5 cm origin Marked dilatation of the LV observed with an increase in trabeculation and significant thinning of the wall Heart weight was 498 grams There is an extensive and dense fibrotic plaque at the lateral aspect of the wall and smaller fibrous plaques dispersed through the musculature The apex of the LV is translucent as a result of thinning of the foliaceous type consisting of collagenous connective tissue



Fig 2 Aneurysmal dilatation 4 by 3 cm located at the posterosuperior zone of the LV wall immediately below the AV sulcus As seen from the interior of the LV chamber the wall is translucent at the subvalvular mitral area Wall thickness was 1 mm and consisted of a fibrous plaque Heart weight was 320 grams (A 3199) Dilatation was most marked in the right chambers

Eight of the same 29 human cases had aneurysmal formation as follows at the level of the left ventricular apex in 6 and in the posterosuperior portion of the left ventricle in the subvalvular zone of the mitral valve in 2

Fig 2 (A 3199) shows an aneurysmal dilatation in the superior portion of the posterior wall of the left ventricle When seen from the inside of the left ventricle this area shows translucency of the wall behind and below the posterior leaflet of the mitral valve

Fig 3 (A 3286) is from another case with striking thinning of the left ventricular wall at two places One site is at the apex and the other is in the posterior wall at the level of the atrioventricular sulcus immediately behind the posterior mitral leaflet This zone also shows aneurysmal formation 3 5 cm in diameter which extends through the thinnest area It is important to emphasize that not all the attenuated areas showed aneurysmal dilatations

Thinning and fibrosis were equally evident in the experimental animals Fig 4 is from a dog (EM 178) with a 21-month old infection Fibrotic foci (localized at the subepicardium) are observed at the apices of both the left and the right ventricles more extensively at the inferior portion of



Fig 3 Anteroposterior section parallel to the interventricular septum (A-3786) Marked dilatation of the LV chamber and an increase in trabeculation observed Heart weight was 785 gram Significant dilatation of the free entricular wall seen at the apex and in the superior a pect of posterior wall of the LV The latter one localized below the A V lcu and behind the posterior mitral leaflet shows a 3 5-cm aneurysm Hi to-logically this con isted of dense collagenous connective tissue with i let of muscular fibers undergoing variable degrees of degeneration (Gomori trichrome ×320)



Fig 4 Dog heart (LM1 P8) as seen from its posterior a pect Durat on of S c infection 2 months Marked dilatation of the RV chamber an l to lesser degree of the RA are seen Th nn ng of the wall t the inferior a pect of the anterolateral surface of the RV Intramural thrombus adhered to the endocard um Exten fibrous cons ting of collagen us connective ti ue and muscular islet Fibrotic plaques became confluent near the subep cardium (Gomori trichrome ×1 5)

the anterolateral surface of the right ventricle The ventricular wall is considerably diminished at this level having a thickness of 0 5 mm at the most affected portion

In both the human and animal hearts an attempt was made by the use of serial sections to find vascular changes especially around the compromised tissues Arterial or arteriolar lesions were not found in any of the cases studied No necrotic areas were found in either the sites of wall thinning or in any other myocardial region

*II Microscopic anatomy* Fibrotic foci were found in the markedly thin regions of the free ventricular walls Histologically these were composed of collagen fibers In those cases depicted in Figs 1 and 2 the translucent zones were 1 mm in thickness and were composed of scar connective tissue and scanty inflammatory infiltrates Similarly the marked thinnings observed in the hearts of chronically infected dogs were composed predominantly of collagen fibers and some mononuclear cell infiltrates In some dogs the Leishmanial form of the parasites were present in the myocardial fibers The parasites were not encountered in human hearts

Fig 4 (LXI P8) shows in the anterolateral surface of the right ventricle a 0 5 mm thin area which is formed by dense collagenous connective tissue with some islets of muscular fibers that show various degrees of degeneration and few inflammatory infiltrates

Muscular fibers located within fibrotic tissue were more abundant in the less involved areas These islets of muscle with variable degenerative changes are particularly evident in the subepicardium on the



Fig 5 Transverse section of the superior third of a human heart (N 3185) Marked dilatation of both ventricular chambers and the right ventricular outflow tract is observed Thinning of the LV posterior wall consisting of a fibrous plaque which is most dense at the subendocardium The plaque consists of collagenous connective tissue and muscular islets The latter are scarce in the subendocardium but become numerous as the subepicardium is reached where bundles are more dense and widespread (Gomori's trichrome X250)

other hand fibrous tissue predominates in the subendocardium The mononuclear cell infiltrate was greater in those subepicardial areas in which muscular islets were more numerous

Fig 5 (A 3183) shows a heart with dilatation of both ventricular chambers The posterior wall of the left ventricle is moderately thinner than the posterior wall of the right ventricle It consists of a plaque of dense subendocardial fibrous tissue Histologic study showed fibrous tissue with few inflammatory infiltrates in the subendocardium and collagenous plaques with interposed muscular islets in the subepicardium Variable degenerative changes were observed in the muscular fibers

The microscopic study of the coronary system indicated an absence of atherosclerotic degenerative lesions in both the arterial and arteriolar segments This was also true in the vessels located around the thin fibrotic areas

*III Correlation between histologic and electrocardiographic findings* A study of the morphology of ventricular complexes of supraventricular or ectopic origin demonstrated the presence of areas of fibrosis

Fig 6 is from a patient (A 1731) with chronic Chagas myocarditis The heart weighed 600 grams and showed marked dilatation of all chambers The thickness of both ventricular walls was markedly diminished extensive confluent scars which formed large fibrous plaques were observed at the anterior surface of the left ventricle from the anteroseptal region to the apex An aneurysm 1 5 cm in diameter was observed at this level Equally large fibrous plaques were observed on the anterior surface of the right ventricle becoming more confluent in the trans-trabecular area The electrocardiogram showed first-degree AV block notched full P wave of 0 12 sec duration in the standard leads and diphasic with slow negative phase in Precordial Lead $V_1$ slightly acuminated in Leads II and $V_F$ QRS and P voltages were similar

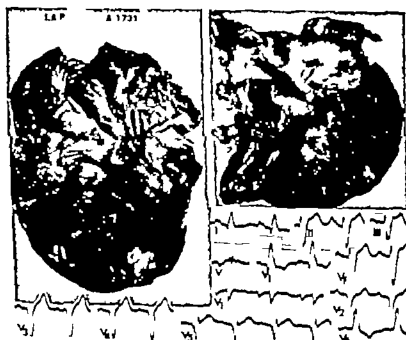



Fig 6 Correlation between histologic and electrocardiographic findings in case A 1731 Ventriculogram shows morphologies of type rS in V ... and QS in $V_5$-$V_6$ indicating ... zone of nonexcitable tissue oriented toward the anterior surface of the heart Marked dilatation of the heart Heart weight was 600 grams Extensive fibrous plaques on the anterior surface of the heart (trabecular zone of RV anteroseptal surface and apex of LV) ... oriented toward the apex shows a discrete positive imbalance of the ST T segment indicating the presence of an aneurysm at the LV apex The coronary system was intact

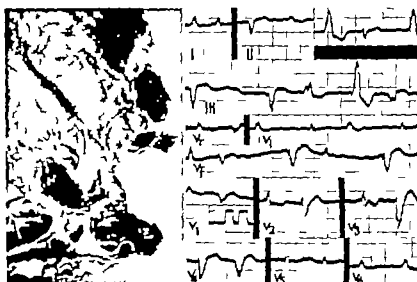



Fig. 7. Same correlation as in Fig. 6 in case N 2199. Extrasystolic ventricular complexes of QS type in $V_1$ and V… and qrS morphologies in $V_F$ indicate the presence of a posteroinferior nonexcitable zone. Extrasystolic QS from V… to V… and the decrease in R in the extrasystolic complex in $V_5$-V… indicate an anteroseptal and LV apical nonexcitable zone. There was thinning and confluent fibrosis in these areas with large irregular plaques in the posteroinferior and anteroseptal aspects and apex of the LV. The positivity of the ST-T in V… V… $V_F$ V… V… corresponds to aneurysmal formation at the apex. The coronary system was intact.

in the left ventricle. These changes correlate well with the marked dilatation observed in both atrial chambers. QS complexes observed in Leads $V_1$ to $V_3$ indicate the presence of an electrically inactive zone throughout the anterior surface of the heart. Histologic sections of the anterior surface of both ventricles demonstrated that the fibrous plaques present consisted of dense collagenous connective tissue with small muscular bundles and few inflammatory infiltrates. The wall was composed exclusively of collagenous connective tissue at the level of the trabeculae and apex of the left ventricle.

The heart depicted in Fig. 7 (N 2199) showed marked dilatation and a decrease in ventricular wall thickness. The wall was 10 mm. thick in the superior portions but decreased to 2 mm. at the apex. There was a diffuse fibrosis throughout the wall and this became interrupted at the apex and at the anteroseptal and posteroinferior surfaces of the left ventricle, forming quite extensive irregular plaques. Several aneurysms with thrombi were observed at the left ventricular apex. The electrocardiogram showed a complete arrhythmia due to atrial fibrillation and frequent multifocal ectopic beats. The extrasystolic morphology is of the QS type in Leads II and III and of the qrS type in Lead $V_F$, indicating the presence of an unexcitable area at the posteroinferior surface of the heart. Extrasystoles of the QS type are observed in Precordial Leads $V_1$ and $V_4$. A significant decrease in the R voltage in the extrasystolic complex is observed from Lead $V_4$ to Lead $V_6$; these changes suggests a nonexcitable zone at the anteroseptal and apical surfaces of the left ventricle. The ventricular wall was found to be formed by dense collagenous connective tissue and a few bundles of muscle fibers forming isolated islets.

The electrocardiographic tracings in animals demonstrated a correlation with those recorded in human beings. Fig. 8 shows the heart of an animal with a chronic infection; there is a marked dilatation and decreased thickness of the free ventricular walls. Fibrous and irregularly distributed plaques are observed on the epicardial surface and at the lateral surface of the right ventricle. The wall is formed by collagenous connective tissue and a few inflammatory infiltrates in the inferior and trabecular regions. Confluent interstitial connective tissue and intermediate muscular islets are seen in the

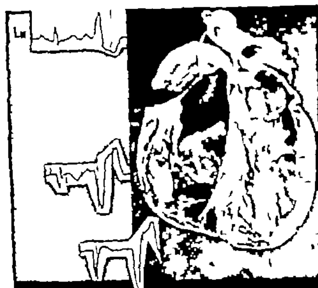



Fig 8 A similar correl t on in a dog with chronic S cru infection of 5 years duration Unipolar epicardial tracings of supraventricular and ectopic entricular origin (RV) obtained at the trabecular zone show mor phologies of the QS type indicating the presence of a nonexcitable zone in the area neighboring the one studied Those of the lateral a pect of the RV w ll show morphologies of QRs type in the supra entricular omplexes and of QS type in those of ectopic origin The trabecular zone consisted of collagenous conn tive tis ue The lateral aspect showed interstitial connective tissue confluent in the subendocardium and subepi ardium form ing dense areas of fibro is The mid portion of the wall showed muscular islets surrounded by collagenou connective tissue The coronary system was normal

subendocardium and subepicardium at the middle zone Unipolar epicardial tracings from the inferior and trabecular zones showed QS morphology in supraventricular or ectopic complexes originating in the right ventricular wall Supraventricular com plexes obtained at the middle zone of the right ventricular wall showed QS morphol ogy Extrasystolic complexes originating in the right ventricle were of the QS type These findings suggest the presence of a nonexcitable zone adjacent to the origin of the leads which coincides with the areas of fibrosis described

## Discussion

Flaccidity and dilatation are commonly seen in chronic inflammatory cardiopathies both in those of S cruzi origin[1 8 17 23] and in those of any other etiology[20 21 24] Flaccidity was found in all of our human and experi mental cases Dilatation of the chambers was marked in 25 of the autopsy cases mod erate in 1 (A 2503) and slight in 3 (A 2769 A 3057 and A 3293) The left atrium was less affected by dilatation in those cases of slight or moderate hypertrophy but showed a dilatation proportion l to that of the other chambers when hypertrophy became marked In 2 of the cases with slight cardiac enlargement (A 3057 and A 3293) the right chambers were affected the most In the third case (A 2769) dilatation w is evident in both ventricles The cases with marked enlargement showed dilatation of all cham bers with no particular pattern of pre dominance

Intramural thrombosis was a frequent finding as demonstrated by Tejeda and Castro[6] and Franco de Oliveira[7] The fre quency of this finding was 79 3 per cent in our study in the human cases with pre dominance of the right chamber (right atrial appendage—RAAp 3 4 per cent RA 58 9 per cent RV 24 1 per cent) as com pared to the left chambers (LA 3 4 per cent LV 51 7 per cent) No thrombi were found in the left atrial appendage (LAAp) or in the right ventricular outflow tract (RVOT) in spite of the marked degree of dilatation evident in both the LAAp and the RVOT Independently of other cham bers the left ventricle showed a higher fre quency of thrombi than did the right ven

tricle, as has been reported previously by Tejada and Castro.[8]

In general, hearts with more marked dilatation showed a greater frequency of thrombosis in the various chambers, although marked cardiomegalies without accompanying thrombosis were also observed (A 3116, A 3183, and A 3247). In general, slight dilatations are not accompanied by thrombosis; in our 3 cases, thrombi were not found in 2 (A 2769 and A 3057), and a left ventricular thrombosis was seen in 1 (A 3293). It was noted that the thrombosis appeared in a left nondilated chamber.

Laranja and associates[27] found that chronically infected dogs showed, after a few months, hypertrophy of the right chambers. In our series, dilatation was found in all chambers in advanced stages of the disease; predominance of the right chamber was observed only in the early phases. Intramural thrombi were found in 11 per cent of the animals with chronic infection, as compared with a higher percentage in human beings; these thrombi were localized 8 per cent in the right ventricle and 3 per cent in the left ventricle.

Thinning of the free ventricular walls was a frequent finding in our autopsy material. Similar findings had been reported earlier in pathologic studies of chronic Chagas' myocardiopathy.[10,11] Dias and associates[1] and Laranja and associates stressed the frequency of thinning at the left ventricular apex; it is produced by confluent fibrosis,[3,4] which subsequently produces aneurysmal dilatation at times.[3,4,6,8] Mori reported the first case with thinning and aneurysmal formation in a different localization. Two of his 3 cases presented the classic findings, but the third one had aneurysmal formation in the anterior surface of the left ventricle below the atrioventricular sulcus. Frequency and distribution of thinning and aneurysmal formation were analyzed from a statistical point of view by Suarez,[19] whose figures are very similar to those in the present study.

Chagas' infection causes in animals (monkeys, dogs, etc.) a degeneration of cardiac fibers and the proliferation of fibroblasts in a relatively short period of time. These changes appeared in some of our animals during the fourth week after primary infection, coincidental with an intense inflammatory infiltrate. Torres and Tavares[18] found that degeneration of cardiac fibers becomes evident 3 months after inoculation in the species *Macacus cebus*. This period can be considered to be a time of expected fluctuation in the appearance of fibrotic lesions in experimental myocardiopathy. Fibrosis appeared very early in some of our dogs, with a decrease in the thickness of the wall being evident 2½ months after the primary infection. Thinning plus extensive fibrosis were more common in the free wall of the right ventricle in experimental animals.

Microscopic study of the thin areas demonstrated that the histologic pattern is the same in human and experimental cases. When thinning is extreme (foliaceous type) and extensive, fibrous plaque is found which consists of collagenous fibers and almost no inflammatory infiltrate. In less extensive lesions, bundles of muscular tissue are seen within the fibrous tissue; these islets show fibers undergoing variable degenerative processes and are more numerous in the cases of less pronounced thinning. Mononuclear cell infiltrate is greater in those areas in which islets are abundant.

Laranja and associates explain the decrease in the thickness of the wall as a result of extensive destruction of myocardial fibers together with replacement by connective tissue. The destruction is the result of a diminishing supply of blood which is in turn secondary to hyperplasia of the intima and thickening of the medial arteriolar layer, with a subsequent reduction in the caliber of the lumen of the vessel. Wainrach and associates[4] interpret the fibrosis as scarred infarcts which result from the inflammation of capillaries, arterioles, and perivascular tissue which produces coronary thrombosis. Coronary or necrotic lesions were not found in our study; therefore, the fibrosis cannot be ascribed to myocardial infarction.

Mori[6] did not find arterial lesions in 2 of his 3 patients but reported moderate arteriosclerotic lesions in the larger coronary branches in the third one, a 52 year old woman. Tejada and Castro[8] failed to find vascular changes in 8 patients with widespread fibrosis. On the basis of all these reports, it is our thought that fiber degeneration and fibrous replacement with subsequent thinning of the wall cannot be

explained by ischemia due to coronary occlusion

Mota[4] believes that the causative factor is the myocardial inflammatory process originated by the disease per se he suggests that the dense fibrosis of limited areas is related to regions in which inflammation and destruction of muscular elements are more intense Pifano and associates[36] and Anselmi and associates[11] demonstrated that the close relationship between the degree of degeneration of muscular elements and the intensity of the inflammatory process in experimental myocarditis originated from alterations in the supply of oxygen caused by increases in the interstitial space due to edema and inflammatory infiltrate In chronic Chagas myocardiopathy it has been possible to demonstrate that rapid ventricular complexes in the electrocardiogram identify electrically nonexcitable zones which correspond to fibrous areas[44, 45] this has been confirmed in our study in both autopsy and experimental series Nonexcitable zones are related to a predominance of fibrous tissue in the areas to which the exploratory electrode is directed Replacement of muscular tissue by collagen fibers caused important changes in supraventricular and ectopic ventricular ventriculograms QR Qr and QS extrasystolic morphologies indicative of nonexcitable zones were the ones most usually observed An analysis of the different leads permitted an appraisal of the localization and extent of the areas of fibrosis The physiopathology of ventricular activation which originates these morphologies has been demonstrated in experimental studies[45, 46] their appearance depends on the presence of ventricular fibrosis or necrosis

In cases of aneurysmal dilatation it was possible to observe the classic positive imbalance of the ST T segment which is pathognomonic of these pathologic findings[44] Even when electrocardiographic findings of ischemia are related to the presence of inflammatory infiltrates in Chagas myocardiopathy[45] the combined presence of nonexcitable tissue and areas of injury should suggest the presence of aneurysms in the wall

## Summary

Pathologic findings in 29 individuals with a clinical picture of chronic Chagas myocardiopathy are analyzed Both macroscopic and microscopic changes are studied and are correlated with similar findings in dogs infected with strains of *Schizotrypanum cruzi*

Flaccidity and dilatation was frequently found in both the human and experimental cases Dilatation was more common in the right chambers of the hearts of the dog particularly in the right ventricle Intramural thrombosis was frequent in human subjects (79 3 per cent) but was observed with less frequency in animals (11 per cent) Thinning of the wall and plaques of fibrosis were found respectively in 72 4 and 42 per cent of the cases in the human and animal groups Parietal aneurysms localized in the areas of fibrosis and thinning were found in 27 6 per cent of the autopsy cases Aneurysms of the wall were not found in dogs but they were seen in the trabecular zone of the right ventricle in 7 animals Aneurysms were of variable diameter (1 to 3 cm ) and disappeared when the animal died Thinning of the wall by fibrous replacement of muscular tissue was found in all of the cases

The histologic pattern of the thin areas was similar in both groups large areas of collagenous connective tissue at the subendocardial level were found Also islets of muscular bundles were found at mid wall and subepicardium They were particularly abundant in the latter localization

An electrocardiographic correlation demonstrated that epicardial unipolar leads obtained at the areas of fibrosis in dogs had the ventricular morphology of nonexcitable zones In human beings ventriculograms of both supraventricular and ectopic ventricular origin always indicated the presence of areas of fibrosis the localization and extent of which could always be determined by an analysis of the different leads

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# Experimental and laboratory reports

## Reduction in cardiovascular and metabolic responses to phenylephrine in acutely pancreatectomized dogs

*Edward Goldberg, M.D.**
*Ira Rosenblum, Ph.D.***
*Albany, N. Y.*

To date a number of diverse factors which can alter the cardiovascular responses to sympathomimetic amines have been reported. Among these are the functions of the endocrine organs, the thyroid gland being one which has recently received much experimental attention.[1] Less attention has been directed to the pancreas despite the known interrelationship between its insulin secretory activity and the secretion of catecholamines by the adrenal medulla.[2]

Some reports in the clinical literature indicate an increased tendency toward hypertension in diabetics, although this may be traceable to such changes as capillary glomerulosclerosis and arteriosclerosis rather than to any altered responsiveness to endogenous catecholamines. Experimentally, however, in alloxan diabetic rats a heightened vascular reactivity to both epinephrine and norepinephrine has been noted.[3]

The purpose of the present experiments has been to investigate a possible relationship between pancreatectomy and the cardiovascular responses to sympathomimetic amines. The acutely pancreatectomized dog was chosen for these studies rather than the alloxan-treated animal because of the well-known ability of alloxan[4] to produce renal lesions which may complicate the interpretation of experimental results. Furthermore, acute pancreatectomy, rather than chronic pancreatectomy, is less likely to cause the development of metabolic disorders, among them acidosis,[5] which itself can alter the cardiovascular responses to sympathomimetic amines.

### Methods

Thirty-nine dogs of both sexes, weighing between 20 and 35 kilograms, were used. These were fasted 16 to 24 hours before the experiment and then were anesthetized with an intraperitoneal injection of 0.67 ml. per kilogram of a solution containing pentobarbital sodium (60 mg. per milliliter), ethyl alcohol (10 per cent volume per volume), propylene glycol (20 per cent volume per volume), and water (Diabutal†).

Tracheotomy was performed and a

From the Department of Pharmacology, Albany Medical College, Albany, N. Y.
This study was supported in part by an Institutional Grant from the Albany Medical College and a grant from the Albany County Heart Association, Inc.
Received for publication Dec. 3, 1965.
*Postdoctoral Fellow, National Heart Institute, United States Public Health Service.
**Public Health Service Research Career Program Award 1-K3-HE-23,420-01, National Heart Institute.
†Diamond Laboratories, Inc., Des Moines, Iowa.

metal T tube was inserted into the trachea. Polyethylene cannulas were placed in the femoral vein for the administration of drugs and in the common carotid artery. The latter cannula was attached to a Statham P23Db blood pressure transducer for the recording of arterial blood pressure. This cannula was also used to obtain samples of arterial blood. After a median sternotomy, artificial respiration was begun with compressed air with the use of a respirator valve. The respirator valve was adjusted by visual observation of the degree of inflation of the lungs.

The pericardium was opened through a lengthwise slit, and a Walton Brodie strain gauge arch was sutured to the surface of the ventricle. The ventricular rate was recorded by applying the electrical output of the strain gauge arch to a heart rate meter. Arterial blood pressure, myocardial contractile force, and heart rate were recorded simultaneously with an ink-writing oscillograph.

*Procedure for pancreatectomy.* The abdomen was entered through a midline incision extending from the xiphoid process to a few centimeters distal to the umbilicus. Clamps were placed around the small intestine at the gastroduodenal junction and about 15 cm distally. The dorsal pancreatic duct, ventral pancreatic duct, cranial and caudal pancreaticoduodenal arteries and veins, pancreatic branches of the splenic and hepatic arteries and veins, and the mesenteric blood vessels were all clamped. The right and left lobes of the pancreas together with the clamped section of the bowel were then excised *en masse*. Hemorrhage was controlled with electrocautery and by clamping.

Sham-operated animals were prepared in much the same way. The bowel was clamped at the identical sites, and the small mesenteric blood vessels were clamped. In addition, other clamps were placed in the abdomen, but these did not occlude the pancreatic ducts or any of the pancreatic blood vessels. The pancreas and bowel were then left in situ. The incisions in the skin were closed with sutures after both surgical procedures had been completed. In both pancreatectomized and sham-operated animals, a period of approximately 90 minutes was allowed to lapse before infusion of a drug was begun.

Samples of arterial blood were drawn into heparinized test tubes at the end of the 90-minute postoperative period and again during the peak of the cardiovascular responses to infusion of a drug. These samples were analyzed for plasma glucose by the Glucostat method, for serum potassium by means of a Technicon Auto-analyzer, and for pH with the use of a blood pH electrode and an Instrumentation Laboratories pH gas analyzer. This latter analysis was performed at 37°C.

The following drugs were used: crystalline zinc insulin (insulin U 40*), *dl*-isoproterenol HCl, and *l*-phenylephrine HCl. The doses of the latter two drugs are expressed as amounts of their free base.

The Student *t* test[9] was used to determine the significance of a difference between groups of animals, and the term "significant difference" is used to denote a P value of 0.05 or less unless otherwise stated.

**Results**

*Effects of infusion of phenylephrine in normal dogs.* Three doses of phenylephrine, 1.0, 3.0, and 10.0 μg per kilogram per minute, were infused for approximately 15 minutes in a total of 12 dogs; 4 dogs were used at each dose level. The cardiovascular changes observed were an increase in systolic pressure and contractile force accompanied by a reduction in heart rate. Hyperglycemia was also produced, particularly by the highest dose of phenylephrine, but no hyperkalemia such as has been reported for other pressor amines[10] was observed. These observations are summarized in Table I. Arterial pH was also measured, and the mean value for all 12 dogs during infusion of phenylephrine was 7.48 ± 0.1 S.E., which was not significantly different from the mean preinfusion control value of 7.50 ± 0.1 S.E.

*Effect of acute pancreatectomy on the responses to phenylephrine.* Acute pancreatectomy was performed in 12 animals. The pancreatectomy resulted in a preparation which did not differ significantly in any of the preinfusion control cardiovascular or metabolic parameters from those measured in normal dogs. Thus, the mean plasma glucose value for all normal dogs was 147 ± 11 S.E. mg. per cent, and that for

*E. R. Squibb & Sons, New York, N. Y.

*Table I Cardiovascular and metabolic responses to l phenylephrine in 12 normal and 12 pancreatectomized dogs**

| *Phenylephrine (µg/Kg /min )* | *Systolic pressure (mm Hg)* | *Contractile force (  Δ)* | *Heart rate (beats/mi  )* | *Glucose (mg /100 c.c )* | *Potassium (mEq /L )* |
|---|---|---|---|---|---|
| Normal | | | | | |
| Control | 114 ± 10 | | 207 ± 05 | 134 ± 09 | 3 9 ± 0 1 |
| 1 0 | 136 ± 12 | | 20? ± 07 | 132 ± 10 | 4 0 ± 0 2 |
| Mean change | +22 ± 03 | 0 | −5 ± 0? | ? ± 0? | +0 1 ± 0 1 |
| Normal | | | | | |
| Control | 113 ± 18 | | ?04 ± 07 | 150 ± 12 | 4 5 ± 0 2 |
| 3 0 | 177 ± 1? | | 188 ± 09 | 172 ± 17 | 4 5 ± 0 3 |
| Mean change | +64 ± 0? | +34 ± 08 | −16 ± 07 | +22 ± 09 | 0 |
| Normal | | | | | |
| Control | 103 ± 10 | | 204 ± 05 | 158 ± 04 | 4 1 ± 0 3 |
| 10 0 | 245 ± 11 | | 178 ± 07 | 240 ± 19 | 4 3 ± 0 2 |
| Mean change | +143 ± 0? | +117 ± 10 | −?6 ± 07 | +8? ± 18 | +0 2 ± 0 2 |
| Pancreatectomy | | | | | |
| Control | 109 ± 18 | | 211 ± 11 | 128 ± 13 | 4 0 ± 0 2 |
| 3 0 | 134 ± 18 | | ?01 ± 12 | 143 ± 12 | 3 8 ± 0 3 |
| Mean change | +25 ± 03† | 0† | −10 ± 04 | +15 ± 10 | −0 2 ± 0 1 |
| Pancreatectomy | | | | | |
| Control | 87 ± 06 | | 20? ± 06 | 155 ± 20 | 3 8 ± 0 1 |
| 7 0 | 154 ± 06 | | 172 ± 09 | 198 ± 29 | 4 0 ± 0 2 |
| Mean change | +67 ± 09 | +52 ± 11 | −30 ± 05 | +43 ± 11 | +0 2 ± 0 1 |
| Pancreatectomy | | | | | |
| Control | 95 ± 08 | | ??1 ± 0? | 216 ± 14 | 4 1 ± 0 1 |
| 10 0 | 179 ± 11 | | 203 ± 02 | 249 ± 16 | 4 1 ± 0 1 |
| Mean change | +84 ± 06† | +66 ± 05† | −18 ± 04† | +33 ± 08† | 0 |

*F  d given  ed  t each d  w  l l-phenylephrine  and  h  values  obt  ined  re expressed  mean ± S E  + d  m  positiv  and  [illegible]

†This mean  [illegible]  the pa  atect  m  ed d  g  d ff red from that observed  ormal d  gs at the same d  se of l phenylephrine  t  P < 0 05

all pancreatectomized dogs was 162 ± 14 S E mg per cent Other control values were systolic pressure 97 ± 2 S E mm Hg for pancreatectomized dogs and 110 ± 2 S E mm Hg for normal dogs heart rate 211 ± 14 S E beats per minute for pancreatectomized dogs and 205 ± 3 S E beats per minute for normal dogs The mean arterial blood pH was 7 45 ± 0 1 S E in the pancreatectomized dogs

These pancreatectomized dogs were infused with one of three doses of phenylephrine either 3 0 7 0 or 10 0 µg/Kg per minute 90 minutes after pancreatectomy A markedly smaller rise in mean systolic pressure was observed in these dogs and this difference is evident in a comparison of the dose response curves of the two types of dogs (Fig 1) Further statistical comparisons between these groups of dogs were made at the two complementary doses of 3 0 and 10 0 µg/Kg per minute These comparisons (Table I) show the occurrence in pancreatectomized dogs of a significant change in response to the effects of phenylephrine on mean systolic pressure heart rate contractile force and plasma glucose at a dose of 10 µg Kg per minute and on mean systolic pressure and contractile force at a dose of 3 0 µg/Kg per minute It is evident therefore that acute pancreatectomy can reduce the cardiovascular and metabolic responses to infusions of phenylephrine

*Partial restoration of the pressor response to phenylephrine with insulin* When the effect of an infusion of 10 0 µg/Kg per minute of phenylephrine on systolic pressure is calculated from observations in pancreatectomized dogs as a per cent of the response in normal dogs a value of 58 ± 5 S E per cent is obtained (Fig 2) Experi

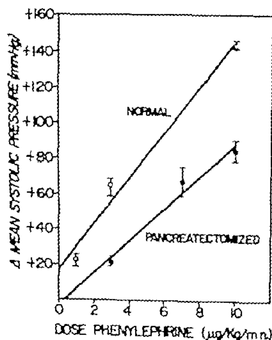



Fig 1 The dose response curves to the pressor response to infusions of graded doses of *l* phenylephrine in 12 normal and 12 pancreatectomized dogs Each point represents the mean ± S E response observed in 4 dogs Each dog was used once for a single infusion of phenylephrine

ments were performed in 9 pancreatectomized dogs with phenylephrine (10 0 μg/kg per minute) to which various amounts of crystalline insulin was added in order to determine whether this pressor response could be restored to that seen in normal dogs Three doses of insulin either 1 2 or 3 units per kilogram were mixed with the dose of phenylephrine and both were infused together The results (Fig 2) show that a dose of 2 units of insulin per kilogram caused a partial restoration of the pressor response to 82 ± 4 S E per cent of normal and this pressor response was significantly greater than that produced in pancreatectomized dogs by 10 0 μg/kg per minute of phenylephrine without the addition of insulin The addition of 1 or 3 units of insulin per kilogram did not however cause a significant restoration of the pressor response to phenylephrine The addition of 2 units of insulin per kilogram although partially restoring the pressor response to phenylephrine produced no significant restoration of the chronotropic or inotropic responses these were a decrease in rate of 30 ± 7 S E beats per minute and an increase in force of contraction of 84 ± 27 S E per cent not significantly different from the decrease in rate of 18 ± 4 S E beats per minute and the increase in contractile force of 66 ± 8 S E per cent observed without the addition of insulin to the infusion (Table I) No consistent changes in plasma glucose occurred from infusion of phenylephrine and insulin in 2 dogs it fell 10 mg per cent and in the third a rise of 79 mg per cent occurred with the addition of 2 units of insulin per kilogram A similar inconsistency was also evident in the pancreatectomized dogs receiving phenylephrine and 1 or 3 units of insulin per kilogram Therefore the expected hyperglycemic effect of phenylephrine must have been opposed by a hypoglycemic effect of insulin in some experiments

*Effects of isoproterenol in normal and*

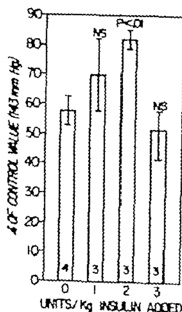



Fig 2 The partial restoration of the pressor response in pancreatectomized dogs to *l* phenylephrine 10 μg per kilogram per minute by the addition of various doses of crystalline zinc insulin The results are expressed as the mean ± S E per cent of the response to infusion of 10 0 μg per kilogram per minute of phenylephrine in normal dogs Where response was significantly different from that observed to phenylephrine without insulin the P value is given NS indicates that no significant difference was observed The numbers in the lower portions of the bars indicate the number of dogs used

*Table II Cardiovascular and metabolic responses to dl isoproterenol in 3 normal and 3 pancreatectomized dogs**

| Isoproterenol ($\mu g$/Kg/min) | Diastolic pressure (mm Hg) | Contractile force (% Δ) | Heart rate (beats/min) | Glucose (mg/100 c c) | Potassium (mEq/L) |
|---|---|---|---|---|---|
| Normal | | | | | |
| Control | 92 ± 12 | | 225 ± 08 | 126 ± 06 | 4 5 ± 0 1 |
| 1 5 | 33 ± 06 | | 249 ± 02 | 259 ± 09 | 3 7 ± 0 1 |
| Mean change | 59 ± 06 | +112 ± 21 | +23 ± 05 | +98 ± 19 | −0 8 ± 0 3 |
| Pancreatectomy | | | | | |
| Control | 95 ± 15 | | 197 ± 12 | 126 ± 06 | 4 0 ± 0 1 |
| 1 5 | 33 ± 11 | | 239 ± 10 | 224 ± 17 | 3 0 ± 0 1 |
| Mean change | −63 ± 01 | +121 ± 10 | +41 ± 03† | +90 ± 17 | −1 0 ± 0 1 |

*Values expressed as mean ± S.E.; + denotes pressor and − depressor change
†The mean change in the pancreatectomized dogs differed from that observed in the normal dogs at P < 0.05

*pancreatectomized dogs* The effects of pancreatectomy on the responses to a vasodepressor amine isoproterenol were studied in 3 normal and 3 pancreatectomized dogs An infusion of 1 5 $\mu$g/Kg per minute of isoproterenol in normal dogs caused an average fall in mean diastolic pressure of 59 ± 6 S E mm Hg (Table II) This response was also accompanied by an increase in myocardial contractile force an increase in heart rate and both hyperglycemia and hyperkalemia (Table II) The same dose of isoproterenol when infused into pancreatectomized dogs caused changes in diastolic pressure contractile force plasma glucose and plasma potassium which were not significantly different from those observed in normal dogs only the increase in heart rate was significantly different from the response in normal dogs

## Discussion

The interrelationship between insulin and the secretion of catecholamines has now been demonstrated in a number of ways One such example is the classic demonstration by Cannon and associates[11] who showed that insulin induced hypoglycemia results in an increased secretion of catecholamines and a subsequent amine induced mobilization of glucose The principal source of the catecholamines which consist mainly of epinephrine would appear to be the adrenal medulla[12] This insulin evoked secretion of epinephrine can evoke a cardiovascular as well as a metabolic response the cardiovascular response has been reported to consist of a fall in diastolic blood pressure and tachycardia[13] Presumably too a reduction in the secretion of insulin should be followed by a reduction in the secretion of catecholamines by the adrenal medulla Thus a feedback mechanism whereby insulin can affect catecholamine supported hemostasis exists in theory

The present experiments have demonstrated that acute pancreatectomy in dogs reduces the cardiovascular and metabolic responses to one pressor amine and thereby extends the connection between insulin and sympathomimetic amines to a drug which does not exist endogenously It is also evident that this interrelationship does not extend to all sympathomimetic amines since the responses to isoproterenol were largely unaffected by pancreatectomy

That these observations with phenylephrine in pancreatectomized dogs involves a deficiency of insulin at least in part is evident from the partial restoration of the pressor response to phenylephrine by the addition of an appropriate amount of insulin It is also evident that other factors among them acidosis could not have been responsible for the reduced response to phenylephrine since our observations clearly show that no significant change in arterial blood pH resulted from acute pancreatectomy Changes in plasma sugar can also be excluded since no significant change in plasma glucose occurred in the 90 min

ates after pancreatectomy Nonetheless there is reason to suppose that subtle changes due to lack of insulin were occurring during this time for Wrenshall and associates[14] have shown that a reduction in the utilization of glucose by skeletal muscle takes place within one half hour after pancreatectomy in dogs and others[15] have shown that the utilization of glucose in rats is decreased within 2 hours after acute pancreatectomy One may speculate then that some manifestation of a deficiency of insulin was present in our pancreatectomized dogs

An important locus at which a deficiency of insulin could be manifested is the cell membrane where insulin acts to facilitate the transmembrane transport of sugars[16] and amino acids[17] including phenylalanine Since phenylephrine resembles the amino acid phenylalanine in structure one could speculate that the reduced responsiveness to phenylephrine resulted from a reduced intracellular penetration in the absence of insulin Evidence now exists that the cardiovascular effects of l phenylephrine are in part derived from the release of endogenous catecholamines[18] which are stored intracellularly[19] The failure of phenylephrine to gain access to these stores would leave only direct adrenergic receptor activation as a mechanism for its diminished cardiovascular and metabolic effects

**Summary**

The cardiovascular and metabolic responses to l phenylephrine were studied comparatively in groups of normal and acutely pancreatectomized dogs Pancreatectomy in dogs had the effect of reducing the rise in systolic pressure myocardial contractile force and plasma glucose as well as causing the reduction in heart rate which was produced by an infusion of phenylephrine 10.0 µg per kilogram per minute The responses to infusion of isoproterenol however were not generally altered by pancreatectomy Of the changes in response to phenylephrine due to pancreatectomy the addition of 2 units of insulin per kilogram to the infusion was able to restore partially the pressor response It may be speculated that these results indicate a role for insulin in facilitating the response to sympathomimetic amines which act to some extent on intracellular stores of endogenous catecholamines

We wish to thank Dr Joseph P Webb The Upjohn Company Kalamazoo Michigan for supplying the heparin sodium U S P used in these experiments

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# Diastolic murmur of equine aortic insufficiency

*David L. Smetzer, D.V.M., M.Sc.**
*Sanford Bishop, D.V.M., M.Sc.***
*C. Roger Smith, D.V.M., Ph.D.****
*Columbus, Ohio*

The literature contains little information concerning either the diastolic murmur or the valvular lesions of aortic insufficiency in horses. That which is available consists primarily of phonocardiograms of the murmurs with little definitive information in regard to valvular lesions.[1-4] Availability of a large population of aged horses and mules at an abattoir has afforded the authors an opportunity for antemortem and postmortem studies of aortic insufficiency in these animals. The purpose of this report is to describe briefly the valvular lesions of aortic insufficiency in horses and mules and to describe the diastolic murmurs accompanying the lesions. A hypothesis of the origin of the presystolic accentuation present in some murmurs is presented.

## Methods

Seventeen horses and 7 mules were selected for study on the basis of presence of a murmur Grade II (of VI) or greater which extended through most or all of diastole. All were over 10 years of age. General health ranged from apparently normal to poor. Others having a soft low pitched murmur restricted to early diastole were not included in the study.

Phonocardiograms (PCG's) were recorded from 19 unanesthetized animals. Murmurs in the other 5 were assessed by auscultation only. Sixteen PCGs were recorded with a Sanborn Twin Beam† oscillograph at a paper speed of 75 mm. per second. Logarithmic filtering was used. A Sanborn crystal microphone with a 1.5 cm. bell was applied to the point of maximal intensity of the murmur. An electrocardiogram (ECG), usually Lead aVF, served as the reference tracing.

Phonocardiograms were recorded from 3 horses with an eight channel Sanborn 550M photographic oscillograph. The filtering system was set at 100 c.p.s. cutoff. Phonocardiograms, ECG, pneumogram and aortic pressure were recorded simultaneously at paper speeds of 50, 100 or 200 mm. per second. Aortic pressure was recorded from 2 horses through polyethylene tubing (0.046 inch I.D.) with a Sanborn model 267B transducer. The left carotid artery was punctured percutaneously with a 14 gauge needle for introduction of a catheter. Aortic or left ventricular

This research was supported in part by [illegible] Health Grant No. HE-08427-08 and Central Ohio Heart Association Grant No. 9-64.
Received for publication Dec. 7, 1965.
* [illegible] of Health Fellow, Department of Veterinary Physiology [illegible] [illegible] University, Columbus, Ohio. Address: [?] [illegible] University College of Veterinary Medicine, 1900 Coffey Rd., Columbus, Ohio 43210.
** [illegible] of Health Fellow, Department of Veterinary Pathology, Ohio [illegible] University, Columbus, Ohio.
*** [illegible] and Chairman, Department of Veterinary Physiology, Ohio State University, Columbus, Ohio.
† [?] Sanborn Company, Waltham, Mass.

pressures were recorded from one horse with a catheter tip transducer* frequency response flat to 100 cycles introduced via a surgically exposed carotid artery

Phonocardiograms were analyzed for the following intensity configuration as determined by variation in intensity and vibration frequency of the murmurs

Hearts were collected immediately after slaughter and transported in an ice chest to the laboratory where they were examined for the presence of valvular and regurgitant or jet lesions Fifteen hearts were examined grossly and microscopically Six hearts were examined for gross lesions only Postmortem examination of 3 hearts was not possible The hearts of 15 horses and mules which did not have a diastolic murmur were examined for valvular lesions and served as controls

**Results**

*Gross pathology* A fibrous band located parallel to the free edge of at least one cusp of the aortic valve was the most consistent and significant valvular lesion found at postmortem examination (Fig 1) A band extended across the entire cusp in some instances In other instances it involved only a portion of a cusp Usually the short bands extended from either commissure of the cusp however in a few instances they were located at the center of the cusp The free edge of those cusps with prominent band lesions appeared to be subject to eversion with insufficiency of the cusp occurring as a consequence Observations supporting this impression will be discussed later Of 21 hearts examined postmortem 18 had significant band lesions on one or more cusps of the aortic valve Bands were located on the aortic cusps of the 18 hearts and distributed in this manner left coronary cusp in 12 hearts right coronary cusp in 3 hearts noncoronary cusp in 2 hearts and both the left coronary and the noncoronary cusps in 1 heart The free edge of each affected cusp was considered to be subject to eversion

Nodules variable in size were found on

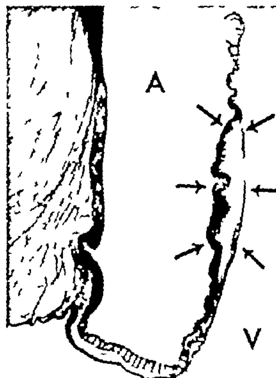



Fig 1 Cross section of an aortic cusp illustrating a band lesion The band is indicated by the arrows The aortic surface is indicated by A and the ventricular surface by V That portion of the cusp distal to the band probably everted after closure of the valve and thereby served as the vibrating structure in the generation of a musical diastolic murmur Orcein van Gieson stain ×7

the ventricular surface or at the free edge of some aortic cusps

No lesion considered as being compatible with the production of a diastolic murmur was found on the tricuspid mitral or pulmonary valves

Jet or regurgitant lesions consisting of irregular masses of connective tissue were present on the interventricular septum (Fig 2) on base of the aortic cusps or on the ventricular surface of the anterior cusp of the mitral valve of 17 of the 21 hearts examined Jet lesions were present on the interventricular septum ventral to the right coronary and noncoronary cusps in 12 of the hearts that had a major band lesion on the left coronary cusp of the aortic valve Minor jet lesions were present on the bases of the right coronary and noncoronary cusps of some of the above mentioned 12 hearts No jet lesion was

*Inductance transducer design 4 by Dr Helmut Ripper Department of Physiology Ohio State University Columbus Oh

Fig [illegible] Regurgitant lesion located on the interventricular septum ventral to the aortic valve of a horse with insufficiency of the left coronary cusp of the aortic valve The point of the arrow indicates prominent cusp-like ridges oriented toward the aortic valve The [illegible] diastolic murmur recorded from this horse is illustrated in Fig 3 [illegible]

found in the thirteenth heart that had a band on the left coronary cusp Jet lesions in the 3 hearts that had a band lesion on the right coronary cusp were located on the base of the left coronary cusp and on the ventricular surface of the anterior cusp of the mitral valve In the 2 hearts that had band lesions on the noncoronary cusps jet lesions were found below the right coronary cusp in one and below the left coronary cusp in the other

Microscopic observations on valvular and jet lesions are described in another report [illegible]

*Diastolic murmurs* Diastolic murmurs were classified as either musical or noisy Interpretation of musicality was based on the relative uniformity in the frequencies of the vibrations comprising the murmur (Fig 3) Those murmurs considered to be noisy were composed of a mixture of vibrations of different frequencies (Fig 4 4)

*Musical diastolic murmurs* Thirteen animals had diastolic murmurs which were completely or predominantly musical A

H11 AoP ECG PCG Pneumo S1 S2 DM insp exp 150 100 50 0

[illegible] (FCG) [illegible] (ECG) [illegible] (Pneumo) recorded simultaneously [illegible] horse with insufficiency of the left coronary cusp of the aortic valve [illegible] used for the catheter in recording aortic pressure Arrows indicate [illegible] aortic pulse [illegible] expressed in millimeters of mercury The amplitude and frequency of the murmur [illegible] The time lines in this and in subsequent illustrations are at 0 04-second intervals

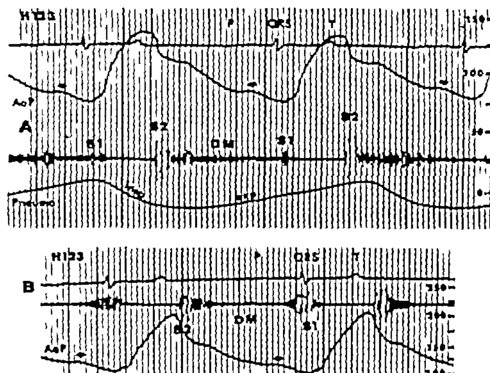



Fig. 4. Electrocardiogram, aortic pressure (AoP), phonocardiogram and pneumogram (Pneumo) recorded simultaneously from a horse with aortic insufficiency. A, Control. B, After intravenous administration of 2 mg of phenylephrine. Aortic pressure recorded through polyethylene tubing and expressed in millimeters of mercury. Reduced sensitivity in B. Arrows indicate dicrotic wave. After the administration of phenylephrine (B) the aortic pressures increased and the murmur became more musical in early diastole and in presystole although retaining noisiness in mid-diastole.

postmortem examination was performed on the hearts of 10 of these. A prominent band lesion was found on at least one aortic cusp in all 10 hearts. By auscultation four murmurs were high pitched with a "cooing" quality (Figs. 3 and 5 A). These probably were comparable to the so-called "sea gull" diastolic murmur in man.[6] The remainder of the musical murmurs were low pitched with a rasping or buzzing quality (Figs. 5 B and 6).

The loudness of the musical murmurs ranged from Grade 2 to Grade 6 with the majority being either Grade 3 or Grade 4. The configuration as determined by a change in the intensity of the murmur during its course was variable from one animal to another. Minor variation was usually observed on a beat-to-beat basis. Peak intensity occurred at the termination of the second sound or shortly thereafter in some animals (Fig. 5 B), in mid-diastole in others (Fig. 5 C), and in presystole in others (Fig. 5 A). Three of the sea gull murmurs increased in intensity uniformly throughout their course. The intensity of another sea gull murmur increased abruptly after the P wave of the ECG (Fig. 3). A prominent band lesion was present on the left coronary cusp of the aortic valve in those instances in which there was presystolic accentuation of the musical murmurs.

In general, the frequency of the vibrations of the musical murmurs was highest at the onset and decreased during the course of the murmur. The frequency of three sea gull murmurs decreased uniformly during their course. The frequency of another sea gull murmur decreased abruptly after the P wave (Fig. 3). The presystolic murmur in one mule was higher pitched than the early diastolic murmur. In some instances it was difficult to establish the precise frequency of a murmur because of faster vibrations being superimposed upon

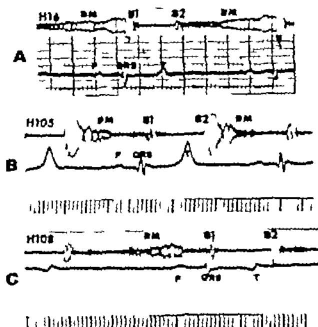



Fig 5 Musical diastolic murmurs (*DM*) of aortic insufficiency recorded from 3 horses Variability of the musical murmur of aortic insufficiency in the horse is well exemplified *A* Configuration of the murmur is generally crescendo with greatest amplitude occurring in presystole *B* Greatest amplitude of the murmur occurs early in diastole followed by a secondary increase in amplitude Murmur is noisy in presystole *C* Musical element restricted to mid-diastole with abrupt termination after onset of P wave Superimposition of vibrations of at least two different frequencies present in the musical element

the slower vibrations of the fundamental frequency (Fig 5 C)

*Noisy diastolic murmurs* In general PCGs of the noisy murmurs were of little value for analysis therefore auscultation was relied upon for assessing most of these Many of the noisy murmurs were loudest at their onset or shortly thereafter and were generally decrescendo throughout Peak intensity in others appeared to occur near mid diastole Ten of the eleven noisy murmurs were Grade 2 in intensity and had a soft blowing quality The intensity of a Grade 3 murmur increased to Grade 6 after the intravenous administration of 2 mg of phenylephrine HCl (Fig 4) In addition it became musical in early diastole and in presystole while retaining its noisiness in mid-diastole A prominent band lesion was found on the left coronary cusp of this horse at postmortem examination A band lesion was found on cusps of the aortic valve in 8 of the 11 horses and mules which had a noisy diastolic murmur

*Other considerations* The loud musical murmurs radiated over a wide area on the thoracic surface thereby making their localization difficult The softer musical murmurs were localized at the second sound area or the left third or fourth intercostal space 3 to 4 inches dorsad to the point of the olecranon In spite of their softness the noisy murmurs could be heard readily over an area extending 2 to 3 inches caudad and ventrad to the second sound area

With two exceptions a distinct precordial thrill was present in all horses and mules which had a musical murmur A thrill was present in only 2 of the animals which had a noisy murmur

The frequency response of the intracardiac transducer used in the catheterization procedure in one horse enabled the instrument to respond to vibrations of the musical murmur that was present (Fig 6) Sonic vibrations sensed by the intracardiac transducer and displayed on the pressure tracing were comparable to those sensed by the microphone on the chest wall The

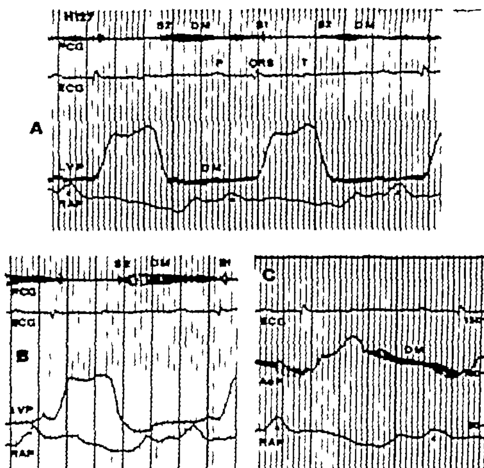



Fig. 6. Phonocardiogram (PCG), electrocardiogram (ECG), left ventricular pressure (LVP), aortic pressure (AP), and right atrial pressure (RAP) recorded from a horse with a diastolic murmur (DM) of aortic insufficiency. Pressures sensed by intracardiac transducers. Aortic pressure (C) recorded at greater sensitivity than left ventricular pressure (A and B). Only the aortic pressure is standardized, expressed in millimeters of mercury. In A, vibrations of the diastolic murmur are superimposed upon the left ventricular pressure tracing. Transducer located in left outflow tract. In B, as the transducer is positioned deeper in the ventricle, some vibrations disappear from the pressure tracing. In C, vibrations of the diastolic murmur (DM) are superimposed upon the aortic pressure tracing when the transducer is positioned near the aortic valve. Presystolic accentuation of the murmur commences near the peak of the right atrial a wave (a).

murmur was recorded best when the transducer was near the aortic valve. Movement of the transducer in either direction from the aortic valve resulted in progressive diminution of the vibrations of the murmur on the pressure tracing.

Fluctuations related to atrial systole were present in the aortic pressure tracings of 2 of the 3 horses catheterized (Figs. 3 and 4). Presystolic accentuation of the murmurs occurred during the course of these atrial waves.

### Discussion

The presence of a band lesion on a cusp of the aortic valve of the hearts of 18 of 21 horses and mules which had a diastolic murmur was indicative of the importance of that lesion in causing aortic insufficiency in those species. A comparable lesion was absent from the hearts of 15 horses and mules which had no diastolic murmur. Eversion of the free edge of those aortic cusps afflicted with a band lesion was usually apparent when the aortic valve was viewed from the root of the aorta. Further evidence that bands resulted in insufficiency was gained by sliding a finger from the base to the free edge on the aortic surface of the affected cusp. The edge of the cusp distal to the band would evert rather than "catch" the finger as did a

normal cusp. Apparently, the band acted as a stricture in preventing the cusp from billowing out in a manner necessary for maintenance of competency of the valve. The fact that jet lesions were found opposite and ventral to a cusp with a band lesion in most cases was more conclusive evidence that band lesions resulted in insufficiency. Significant band lesions were absent from the aortic valves of 3 horses which had a noisy diastolic murmur. Small nodules on the aortic valves of those horses could have resulted in slight insufficiency. Insufficiency was considered to be probable in 3 horses whose hearts were not examined post mortem. This probability was based on the observation that the murmurs in these were comparable to the murmurs in animals proved to have aortic insufficiency.

It is stated that the generation of a musical diastolic murmur is dependent upon the flow of blood past a structure capable of vibrating freely in a periodic manner.[5] Sagging and eversion of an aortic cusp, usually the right anterior one, is a common cause of musical diastolic murmurs in man.[5,7] It has been reported that the presence of bands on an aortic cusp leads to eversion of the cusp and the consequent generation of a musical diastolic murmur in man.[8] An everted aortic cusp was probably the source of the musical diastolic murmurs in our study, since postmortem examination in each case revealed the presence of a band lesion which appeared to permit eversion of the cusp. Why the murmur was noisy in other instances in which an everted cusp was the apparent cause of insufficiency is not immediately evident. Perhaps in some of these the murmur was musical at one time, but because of a progressive change in the valvular lesion the murmur became noisy. The amount of regurgitation, the position of the everted cusp relative to the regurgitant stream, and the thickness and width of the everted edge are factors which probably enter into determining whether the murmur is musical or noisy, and its frequency if musical.

Jet lesions have received consideration as a site for the production of murmurs. It is theorized that the roughened surface of the jet lesion is capable of generating audible vibrations as a consequence of the impact of a regurgitant stream of blood. It might be significant that the septal jet lesions of 3 horses which had a sea gull type of murmur were composed of cusp-like ridges oriented toward the aortic valve (Fig 2). No jet lesion was found in another horse which had a comparable murmur, however.

Presystolic accentuation was one of many interesting features of the musical murmurs. In man, a diastolic murmur of pure aortic insufficiency that is accentuated in presystole is referred to as an Austin Flint murmur.[10,11] It is believed that the regurgitant stream of blood from the aortic valve strikes the anterior cusp of the mitral valve and displaces it into the stream of blood coming from the contracting atrium. By being subjected to *two opposing streams of blood*, the anterior cusp of the mitral valve is considered to vibrate and thereby generate the audible vibrations of the Flint murmur.

An everted aortic cusp was considered to be the origin of both the early diastolic and the accentuated presystolic musical murmurs in the horse and mules studied for the following reasons. (1) Presystolic accentuation of the murmur occurred in the absence of jet lesions on the anterior cusp of the mitral valve of some horses. In these, jet lesions on the ventricular septum indicated that insufficiency was not a recent development. From this the importance of the anterior cusp of the mitral valve as the site of origin of the accentuated presystolic murmur of horses becomes open to question. (2) Localization of a musical murmur (accentuated presystolic element included) at the aortic valve by an intracardiac transducer in one horse (Fig 6) indicated that the everted left coronary cusp found at necropsy was the origin of both the diastolic and presystolic murmur in that particular case. (3) A presystolic musical murmur was *never present unless preceded by an earlier* musical murmur, suggesting a common site of origin for the two. It seems to be likely that, if the presystolic musical murmur had as its origin some vibrating structure other than an everted aortic cusp, there would be instances in which the murmur is noisy in early and mid-diastole and musical in presystole.

It is apparent that at the time of atrial systole the character of the musical mur-

cent NaCl in distilled water) solution. The lobe was immersed in a saline-filled bottle which was then sealed (Fig. 1). The four cannulas were connected with pipes which passed through the rubber stopper of the bottle, with care taken so that the entire system was free of air. The perfusion pressure gradient was the drop in pressure in centimeters of saline from the fluid level of the pulmonary arterial reservoir to that of the venous reservoir. Vascular conductance was calculated as the flow in liters per minute per centimeter of saline of the arteriovenous pressure difference. Moment-to-moment displacement of fluid from or into the airway or pleural spaces was indicated by movement of a fitted plastic ball marker in horizontal tubes connected with the bronchial or pleural spaces. Airway and pleural pressures were held constant by means of siphons and overflow reservoirs to which they were connected. The transpulmonary pressure was established by setting the level of the pleural pressure at either 2.5 or 4 cm. below the airway pressure level. The pulmonary venous outflow was measured with a graduated cylinder and stopwatch. Other details have been described.[1]

The data obtained included the empty wet weight of the lung lobe under study, the levels of the reservoirs attached to the arterial, venous, airway, and pleural connections, the rate of flow through the vascular system, and the rates of movement of fluid into or out of the airway and pleural compartments.

Studies were made of the effect of (1) variations in arterial pressure as the venous pressure was held constant, (2) equal changes in both arterial and venous pressure levels, thus holding the arteriovenous pressure difference constant, and (3) variations in venous pressure as the arterial pressure was held constant.

**Results**

Analysis of the results on the three series of experiments revealed that all of the accumulated data, which at first sight appeared to be dissimilar, could be treated in a consistent and comparable manner by considering the airway pressure to be the zero reference level (Fig. 2). The data are analyzed in terms of whether conductance was zero, basal, intermediate, or maximal.

*Zero conductance.* Flow and conductance were zero in all tests in which airway pressure exceeded both arterial and venous pressures (Fig. 3). Since there was no flow

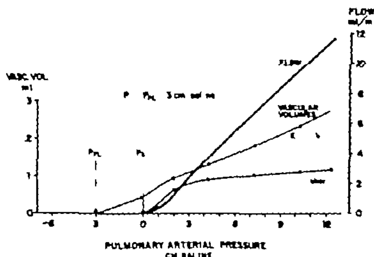



Fig. 2. Effect of vascular pressure on vascular volumes and flow. Values are per gram of empty wet lung lobe. The pressure in the arterial reservoir is given in the horizontal axis. Airway pressure ($P$) is the zero reference. In the experiment shown, venous and pleural pressures are both set at 3 cm. below airway pressure. Vascular volumes are given in the vertical axis on the left. Extralobar vascular volume shows an increase in volume when arterial pressure exceeds pleural pressure, as indicated in the upper light line. The lower light line gives the intralobar vascular volume as arterial pressure is raised. Flow is given in milliliters per minute in the right vertical axis and in the heavy line. Discussed in text.

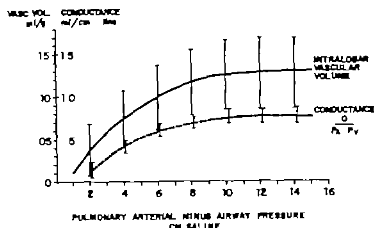



Fig. 3 Relationship between intralobar vascular volume and vascular conductance (Pv > PPL). In this set of experiments on six dogs mean values are given by the curves and standard deviations by the vertical lines. The scale on the left of the vertical line is vascular volume in milliliters per gram of lung lobe. The scale on the right of the vertical line is conductance in milliliters per minute per centimeter of saline. The horizontal axis is the height of the pulmonary arterial pressure above airway pressure in centimeters of saline.

despite an arteriovenous pressure gradient the absence of a functioning communicating channel between the arterial and venous reservoirs was indicated. As long as the arterial reservoir remained lower than the airway reservoir there was no displacement of fluid from the airway.

*Basal conductance.* As the arterial pressure was raised slightly above the airway pressure a rapid movement of the indicator ball in the horizontal tube connected to the bronchus showed that fluid was displaced from the airway compartment and flow through the vascular bed began. The indicator ball came to approximate rest within 1 minute after the alteration in the arterial pressure. When the arteriovenous pressure difference and the airway pressure were held constant for 20 minutes or more the rate of flow also remained constant.

When venous pressure was lower than pleural pressure oscillations of the entire system with a recurrence rate of 1 to 3 per second were observed. The oscillations stopped when venous pressure was raised to pleural pressure; conductance increased slightly at this time.

*Intermediate conductance.* When pulmonary venous pressure was negative progressive elevation of the arterial pressure above zero displaced fluid from the airway and conductance increased above basal values. At an arterial pressure of about 7 cm of saline an amount of fluid equal to about 14 per cent of the empty wet weight of the lung lobe was displaced from the airway (Figs. 2 and 3).

*Maximal conductance.* When arterial pressure was more than 7 cm of saline above airway pressure and venous pressure was more than 4 cm of saline above airway pressure additional elevations of arterial pressure up to 13 cm of saline had no further effect on the displacement of fluid from the airway or on the conductance (Fig. 3). Flow increased approximately linearly with the arteriovenous pressure difference. At arterial pressures higher than 13 cm of saline fluid was displaced from the airway at a continuous rate. At 15 cm of saline the continuous rate of displacement became very rapid.

*Relationship between airway displacement and vascular conductance.* Vascular conductance increased in direct proportion to the volume of fluid displaced from the airway (Figs. 3 and 4). Conductance was increased as the venous pressure was elevated above airway pressure until venous pressure was 4 cm of saline; further elevations of venous pressure had no effect on conductance.

In some experiments arterial pressure was held constant while venous pressure was elevated by increments from subpleural pressures (Fig. 4). When venous

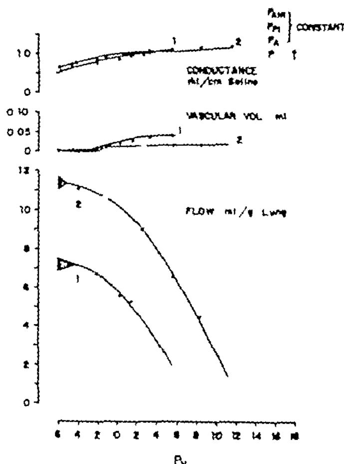



Fig. 4. The effects of the tr n pulmonary pressure on flow rate intralobar vascular volume and conductance. Flow rate per minut gi en in the lower ertic l axis labeled *ml/g*. Conductance is given in the upper scale. Intralobar d placement per gram of lung on the middle ertical scale. Pressures were held constant in the pulmonary artery nd in the air ay and pleural spaces. In experiment *1* $P_A$ = 7.0 cm of saline and $P_{PL}$ = 3.5 cm of saline. In experiment *2* P was 12.0 and $P_{PL}$ was −3.5 cm. Pulmonary enou pressure ($P_V$) is given in the horizontal axis. When pulmonary enous pressure was −6.0 cm the ph te indic tors and entire lung lobe showed oscillations (flutter) w th a recurrence rat of 116 per minute in experiment *1* nd a r te of 108 per minute in experiment *2*. The oscillations are indicated by the widened line. The oscillations ceased when venous pressure was raised to the pleural pressure level. With further increments in pulmonary nous pres ure intra lobar ascular olume increased and flow rate decreased in accord with the decreased arteriovenous pres ure gradient. Flow approached zero as enou pres ure equaled arterial pressure; the conductance and fluid dis placements were maximal at this le el as the intralobar vascul r volume reached almost steady levels. Va cular conductance aried with the intralobar vascul r olume. The volume entering the intralobar e sels is less than in Figs. 2 and 3 since the ntralobar vessels were already partially opened by the high pulmonary arterial pre sures. The increases in intralobar ascular volume in experiment *1* were gre ter than in experiment *2*. I tra lobar vascular olume effects re not gi en.

pressure was less than pleural pressure oscillations of the entire system were ob served and conductance was small. As pul monary venous pressure was raised the oscillations ceased an increment in dis placement of fluid from the airway com partment was observed and conductance approached maximal values. When the displacement of fluid from the airway be came maximal conductance also became maximal.

The rate at which the conductance changed as filling of the intralobar vessels took place is illustrated in Fig. 5. In these experiments some of the parameters are held constant while others are changed. In the upper line the arteriovenous pressure gradient the airway pressure and the

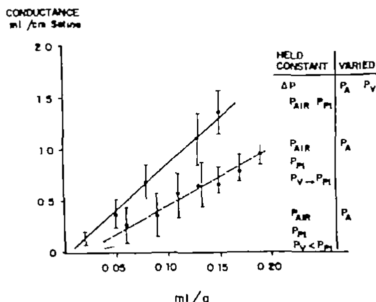



Fig 5 The relation hip between intralobar vascul r olume and conduct nce The vertical axis giv e conductance in milliliters per minute per centimeter of saline the horizontal axis gives intralobar vascul r olume in milliliter per gram of lobe In the upper line the vascular pres ure was increased by the simultaneous increase in arterial and venous pressures maintaining a constant arteriovenous pressure gradient of 3 0 cm I the middl line the arterial pressure w increased while airw nd pleural pres ures were held constant venou pres ure was raised to ard the pleural pres ure level Similar condition held in the lower l ne except that venou pressure was held con tant at 3 cm or more below the pleural pressure In all experiments ascular conductance increased with intralobar ascular olume However the effect varied with the level of the enous pressure Conductance was maximal when venous pressure exceeded airw y pressure The dots on the two sets of upright lines repre ent mean alues The vertical l nes give the standard deviations

pleural pressure are all held constant The arteriovenous pressure difference is held constant by varying the arterial and venous pressures by equal increments As arterial and venous pressures are raised the volume displaced from the airway (milliliters per gram) is directly proportional to the conductance This effect varies with the level of the venous pressure

In the middle line of Fig 5 airway pleural and venous pressures are held constant Venous pressure was slightly less than or equal to pleural pressure only the arterial pressure was varied The displacement from the airway varied directly and in a linear manner with the conductance with a reduced slope

The dashed line gives data obtained when airway pleural and venous pressures are held constant venous pressure is lower than pleural pressure Increases in the arterial pressure were associated with displacement of fluid from the airway with changes in conductance

The solid dots in Fig 5 represent mean values obtained in the six experiments The vertical lines represent the standard deviations of the conductance as volume was displaced from the intralobar compartment

*Effect of transpulmonary pressure* The effects of intralobar volume and of the resulting geometric effects on the pulmonary vasculature were examined by lowering the pleural pressure from −2 to −4 0 cm (Fig 6) The increase in transpulmonary pressure was associated with enlargement of the extralobar vascular volume in accord with the greater transmural pressure acting on the extralobar vessels Conductance was not affected

## Discussion

The results are discussed in terms of varying levels of vascular conductance and in terms of the mechanical forces which affect conductance

*Zero conductance* The absence of flow despite a drop in pressure from the arterial

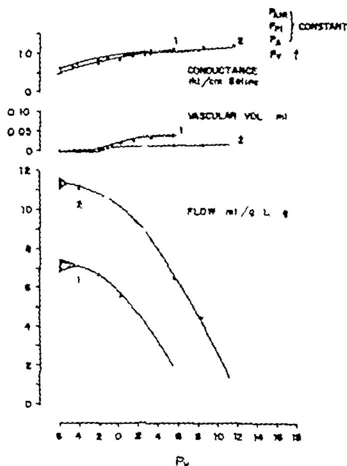



Fig. 4. The effects of the transpulmonary pressure on flow rate, intralobar vascular volume, and conductance. Flow rate per minute is given in the lower vertical axis labeled ml/g. Conductance is given in the upper scale. Intralobar displacement per gram of lung is on the middle vertical scale. Pressures were held constant in the pulmonary artery and in the airway and pleural spaces. In experiment 1, $P_A$ = 7.0 cm. of saline and $P_{PL}$ = 3.5 cm. of saline. In experiment 2, P was 12.0 and $P_{PL}$ was −3.5 cm. Pulmonary venous pressure ($P_V$) is given on the horizontal axis. When pulmonary venous pressure was −6.0 cm., the plastic indicators and entire lung lobe showed oscillations (flutter) with a recurrence rate of 116 per minute in experiment 1 and a rate of 108 per minute in experiment 2. The oscillations are indicated by the widened line. The oscillations ceased when venous pressure was raised to the pleural pressure level. With further increments in pulmonary venous pressure, intralobar vascular volume increased and flow rate decreased in accord with the decreased arteriovenous pressure gradient. Flow approached zero as venous pressure equaled arterial pressure; the conductance and fluid displacements were maximal at this level as the intralobar vascular volume reached almost steady levels. Vascular conductance varied with the intralobar vascular volume. The volume entering the intralobar vessels is less than in Figs. 2 and 3 since the intralobar vessels were already partially opened by the high pulmonary arterial pressures. The increases in intralobar vascular volume in experiment 1 were greater than in experiment 2. Extralobar vascular volume effects are not given.

pressure was less than pleural pressure, oscillations of the entire system were observed and conductance was small. As pulmonary venous pressure was raised, the oscillations ceased, an increment in displacement of fluid from the airway compartment was observed, and conductance approached maximal values. When the displacement of fluid from the airway became maximal, conductance also became maximal.

The rate at which the conductance changed as filling of the intralobar vessels took place is illustrated in Fig. 5. In these experiments some of the parameters are held constant while others are changed. In the upper line, the arteriovenous pressure gradient, the airway pressure, and the

As the arterial pressure increased above the airway pressure a small volume of fluid was displaced from the airway compartment and flow began The displacement can be accounted for as a slight filling of the intra-alveolar capillaries If all the capillaries in a lobe were identical all the vessels would be slightly opened

*Maximal conductance* When the displacement of fluid from the airway is maximal as it arterial pressures of 7 cm or more of saline conductance becomes maximal It may be assumed therefore that this pressure is sufficient to fill the capillaries of the alveolar spaces In this range of fully filled vessels the linear relationship between perfusion pressure and flow shows that the Hagen Poiseuille law originally developed for flow through glass tubes applies to the pulmonary capillary Since further elevations of arterial pressure up to 13 cm of saline have no effect on conductance it may be assumed that filled alveolar capillaries are nondistensible within this range of pressure This suggests that the capillary structure is supported by sufficient material to prevent stretching at least up to a transmural pressure of 13 cm of saline The previously reported sudden increase in the rate of displacement of fluid from the airway when arterial pressure exceeds 13 cm of saline[13] suggests that ballooning has occurred and that a threshold to filtration may have been breached presumably by some fundamental change in the characteristics of the capillary wall These findings also indicate that the use of transmural pressures as high as 15 cm of saline applies abnormal stresses to the pulmonary vessels[4] and may introduce significant artefacts

*Intermediate conductance* Conductance varied with the volume of fluid displaced from the airway compartment and with the presence of oscillations in the system At intravascular pressures slightly higher than airway pressure the capillaries apparently open partially and flow begins Further increments in vascular pressure up to 7 cm of saline displace more fluid from the airway presumably as a result of the passive filling of the intra-alveolar capillaries Conductance increased with the opening of the vessels as indicated at the point of maximal displacement of fluid from the airway (Figs 3 and 5) The close relationship between displacement and conductance is indicated by the fact that both factors reached maximal values at the same time

*Pressure flow interrelationships* Nonflow experiments showed a maximal displacement from the airway at an intravascular pressure of 4 cm of saline[1] The displacement in the flow experiments was considerably reduced and seemed to vary with arterial venous and airway pressures and with the rate of flow (Figs 5 and 6) These effects could be attributed at least in part to the likelihood that in flow a portion of the total energy becomes manifest as velocity or is lost as a result of friction Because of these losses of pressure the capillaries are not completely filled and conductance is less than maximal until the arterial pressure is above 7 cm of saline

As stream velocity increases the fall in intravascular pressure may lower the transmural pressure to zero and thereby result in collapse of the vessel With collapse velocity becomes zero intravascular pressure rises sharply and redistends the vessel so that flow begins again As the stream velocity increases the conditions for closure are again established and a recurrent cycle of opening and closing (flutter) of the vessel is generated Conductance varies during each cycle from a maximum when the vessel is completely open to a minimum of zero when it is closed Opening and closing in phase of all vessels of the lung lobe produces marked oscillations of the system The flow and the calculated average conductance increase with the proportion of the time that the vessel is open (duty cycle) On the basis of physical considerations collapse occurs at the site of the lowest transmural pressure at the downstream segment of the collapsible vessel The latter is probably more likely to occur in intralobar (alveolar) vessels since transmural pressure is lower in the vessels of the airways than in the vessels facing the pleura Recurrent opening and closing of the pulmonary capillaries of the rabbit lung originally observed by Wearn and associates[12] has been confirmed by numerous other workers Diffusion studies in patients and in the isolated lung had led Lewis and coworkers to state tha

capillary segments may be open or closed

*Arterial pressure.* An elevation in arterial pressure and inflow also raises the pressure throughout the system. When the rise is sufficient to increase the transmural pressure at the downstream end of the capillary to positive values, vascular collapse is inhibited and conductance becomes maximal.

*Venous pressure.* Elevation of the pulmonary venous pressure sometimes results in an increase in pulmonary vascular conductance. In previous studies[14, 7] this laboratory has indicated that this may result from the more complete filling of previously collapsed vessels. When the vessels are partially collapsed, elevation of the venous pressure raises the intravascular pressure and produces a more positive transmural pressure which rounds out the vessels, inhibits flutter, and increases vascular caliber and conductance to a maximum.

Similar effects of increasing flow associated with an elevation of the downstream pressure have subsequently been noted in systemic vascular beds by Burton[22] and for the pulmonary bed by Lloyd,[8] Borst,[20] Carlill,[21] Banister,[24] Haddy, and Campbell[25] and their co-workers. These workers did not measure the concomitant changes in vascular volume.

When the pulmonary capillaries are fully distended and conductance is maximal, further increases in arterial or venous pressures, or in flow, have no further effects on vascular conductance.

*Blood flow.* Increases in pulmonary blood flow in the air-filled lung are known to increase the pulmonary arterial pressure only slightly, a response usually attributed to an active dilatation of the pulmonary vasculature. It is suggested that the increase in conductance may represent the passive opening of previously collapsed alveolar capillaries in the more elevated segments of the lung. Thus a very slight rise in intravascular pressure can open many new channels and enhance pulmonary vascular conductance without invoking smooth muscle relaxation.

*Airway pressure.* Factors which affect airway pressure even slightly may play important roles in the regulation of pulmonary vascular conductance.[26] In the absence of ventilatory movements, airway pressure remains constant at atmospheric pressure. During normal ventilation the intralobar pressure oscillates over a range of a few centimeters of saline. These small changes in pressure can determine whether at a given moment the transmural pressure of some of the capillaries in the air-filled lung is positive and conductance and volume are maximal, or whether the transmural pressure is negative and the collapsed capillaries provide zero conductance. Thus, the elevated airway pressure in expiration may be considered to collapse vessels and decrease conductance. Larger variations in airway pressure are developed during dyspneic grunting, and coughing.[20]

*Effect of gravity.* In the air-filled lung, the transmural pressure tends to be more positive in the more dependent portions than in the more elevated portions. The dependent portions, therefore, have higher vascular conductances and flows. In an air-filled lung, an increase in airway pressure as occurs in expiration can generate a wave of collapse of the capillaries which sweeps from the more elevated to the more dependent capillaries of the lobe. In the present preparation, hydrostatic effects are eliminated and all capillaries probably open and close together. This technique eliminates the wide spectrum of the degrees of openness or collapse of the intra-alveolar vessels observed in the air-filled lung. As a result, small differences in pressure produce relatively large effects on conductance.

The changes in conductance given above have generally been explained as being due to either vasodilation or to distention of the caliber of the pulmonary vessels. Borst[9] observed that the change in conductance is less notable when arterial or venous pressure is high. Harasawa and Rodbard[16] have shown that the effect is most marked when the pulmonary venous pressure approaches airway pressure. The present results indicate that conductance changes as the caliber of the capillaries varies with transmural pressure. These effects are remarkably similar to those exhibited by a soft-walled passive collapsable tube.[4, 27, 28]

As transmural pressure became progressively less positive, as by a lowering of venous or arterial pressures, or a raising of airway pressures, fluid was displaced into the airway, indicating partial collapse of

the pulmonary capillaries and conductance was reduced Under these circumstances conductance increased with small increases in venous or arterial pressure or reductions in airway pressure (Figs 2 and 3) These effects might be misinterpreted as a vasodilator response although mechanical effects at the collapsible capillary can readily account for them

The foregoing analysis clarifies the definite but limited effects on conductance of changes in arterial venous and airway pressures and of flow It is suggested that these effects on conductance are determined ultimately by their hydrodynamic effects on the cross sectional area of the capillary bed

The present data support the concept that capillary transmural pressure determines the effective cross sectional area and conductance of the vascular bed in the lung[11] as well as in other structures[4]

## Summary

Vascular conductance (flow rate per unit of arteriovenous pressure gradient) was studied in the degassed lung lobe in which saline solution was used to fill the airway and the pleural space and to perfuse the blood vessels at selected arterial and venous pressures This preparation eliminated effects due to surface osmotic and hydrostatic forces those due to geometric relationships resulting from distention of the lung and those which result from oscillations of pressures in the airway and in the vessels

All the data obtained could be treated in a consistent manner by considering the airway pressure to be the zero reference level The phenomenon of critical closing could be demonstrated as a mechanical effect due to negative transmural capillary pressure thus when airway pressure exceeded arterial and venous pressures conductance was zero As arterial pressure was raised above airway pressure fluid was displaced from the intralobar (airway) compartment Conductance was correlated directly with the volume of displacement of fluid from the intralobar compartment These data indicated that intralobar vessels presumably the alveolar capillaries opened when transmural pressure was positive and closed when it was negative

Variations in conductance occurred with changes in transmural pressure Positive transmural pressures were produced by elevations of arterial or venous pressures or by a lowering of airway pressures When intralobar capillary transmural pressure was about +7 cm of saline conductance was maximal

Changes in the degree of filling of the lung lobe or in the volume of fluid in the vessels exposed to the pleural surface had no significant effects on conductance

Recurrent oscillations of the system were observed at transmural pressure of approximately zero These oscillations were similar to the patterns of recurrent closure and opening of soft walled vessels (flutter) noted in previous studies Conductance was proportional to the period during which the vessel was open (duty cycle)

It is shown that marked changes in pulmonary vascular conductance can be produced by mechanical effects at the collapsible intra alveolar capillary Before changes in conductance can be attributed to humoral neurogenic or pharmacologic factors the potential mechanical effects on conductance of changes in transmural pressure at the capillary must be controlled

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# Pulmonary angiography in experimental pulmonary embolism


*James E. Dalen, M.D.**
*Virendra S. Mathur, M.D.***
*Hilary Evans, M.D.****
*Florence W. Haynes, Ph.D.*
*Ali A. Pur-Shahriari, M.D.*****
*Paul D. Stein, M.D.***
*Lewis Dexter, M.D.*
*Boston, Mass.*


Pulmonary thromboembolism is being increasingly recognized as one of the most common causes of death in the hospitalized population.[1] Effective therapeutic and prophylactic measures are available but their implementation demands accurate recognition of this disorder.

The use of pulmonary angiography as an aid to the diagnosis of pulmonary embolic disease has been recent.

As early as 1952 Lochhead and associates[2] reported that pulmonary angiography can demonstrate gross abnormalities in the pulmonary vasculature of dogs minutes after they are embolized with autologous blood clot. In 1954 selective pulmonary angiography was used by Aitchison and McKay[3] to demonstrate pulmonary thromboembolic disease in a patient. Yet it has only been within the past several years that some investigators[4-7] have begun to include this technique as an integral part of the diagnostic work-up of patients suspected of pulmonary embolism.

The recognition of evidence of thromboembolism by angiography in man is fraught with difficulty. Control angiograms are not available to distinguish possible variations in the normal pulmonary vasculature from abnormalities due to embolism. Angiographic abnormalities due to embolism must be distinguished from abnormalities that are due to the frequently coexistent cardiac and pulmonary disease. The possible changes in the angiographic appearance of sequelae of thromboembolism that may occur with the passage of time are not known.

This study was undertaken to determine the immediate and sequential changes oc


From the Departments of Medicine and Pathology, Peter Bent Brigham Hospital and Harvard Medical School, Boston, Mass.



This work was supported in part by grants from the Life Insurance Medical Research Fund, the National Heart Institute, United States Public Health Service (Grants HE 00430, HTS-5334, HE [illegible], and HE [illegible]), and the American Heart Association.

Received for publication on Dec. 20, [illegible].



*Work done during the tenure of a Postdoctoral Research Fellowship from the National Heart Institute, National Institutes of Health. Present address for correspondence: James E. Dalen, M.D., Peter Bent Brigham Hospital, 721 Huntington Ave., Boston, Mass. 02115.
**Research Fellow (supported by National Heart Institute Training Grant HTS-[illegible]).
***Resident in Pathology, Peter Bent Brigham Hospital, and Teaching Fellow in Pathology, Harvard Medical School.
****Research Fellow (supported by National Heart Institute Training Grant HTS-[illegible]).

curring in the angiographic appearance of the pulmonary vasculature of the normal dog when pulmonary thromboembolism is induced in such a way that the size and the location of the emboli are known and can be confirmed by postmortem examination.

#### Methods

Pulmonary embolism was induced in 23 closed-chest mongrel dogs weighing from 11 to 20 kilograms (median 15 Kg.). Anesthesia was induced by intraperitoneal pentobarbital, 32 mg. per kilogram of body weight. The dogs were intubated and ventilated with room air by a Starling pump with a tidal volume of 300 ml. and a rate of 30 respirations per minute.

Six dogs were embolized with autologous blood clot produced by the method described by Lochhead and co-workers. An 11 cm. to 13 cm. segment of the left external jugular vein was isolated and occluded; then 1.0 ml. of thromboplastin* extract was injected into the isolated vein segment. An average of 3.0 ml. of clot was thus formed and was released after the vein had been occluded for 30 minutes.

Seventeen dogs were embolized with autologous blood clot rendered radiopaque by a modification of the technique of Allison and colleagues.[8] Four milliliters of Dionosil,† 1 ml. of 10 per cent $CaCl_2$, and 2 ml. of thromboplastin extract as a mixture was added to 9 ml. of autologous venous blood, mixed thoroughly, and then immediately transferred to a glass tube with an internal diameter of 4 mm. After 60 to 120 minutes at room temperature, 2 to 6 ml. of the resultant radiopaque clot was introduced into the left external jugular vein.

Hemodynamic, angiographic, and radiographic studies were performed before, minutes after, and at intervals varying from ½ hour to 24 hours after embolization (Table I).

In each control and follow-up study, pulmonary and femoral arterial pressures were recorded with a Sanborn recorder by means of P23d Statham strain gauge manometers; the electrocardiogram (Lead II) was monitored, and selective pulmonary angiography in at least two projections was performed. For each dog, target-to-film distance was held constant by taking each angiogram with the film 2 cm. above the anterior chest. Two hundred and eighty angiograms were recorded and assessed. In the 17 dogs embolized with radiopaque blood clot, plain chest x-ray films were taken to identify the location of the radiopaque thromboemboli.

Selective pulmonary angiography was performed by the single-film technique. With a No. 8 Rodriguez-Alvarez catheter positioned in the main pulmonary artery or the right ventricular outflow tract, 1.5 ml. per kilogram of body weight of 75 per cent Hypaque M* was injected by a Cordis injector at a rate of 30 ml. per second. Angiograms were taken at the peak of the arterial phase of the passage of contrast medium through the pulmonary vasculature.

This technique of angiography allowed identification of all vessels larger than third-order arteries, using the Edwards[9] and Brenner[10] classification of the pulmonary vasculature (Table II).

Immediately prior to sacrifice after the last follow-up study in each experiment, 10,000 U.S.P. units of heparin‡ was given intravenously. The heart and lungs were removed en bloc. The lungs were inflated by introducing saline into the trachea at a pressure of 10 cm. of saline and then, in dogs embolized with radiopaque blood clot, plain roentgenograms were taken in order to visualize the emboli. In all 23 dogs postmortem pulmonary arteriograms were recorded by the method of Smith and co-workers.[11] This technique allows identification of the elastic arteries and all four subdivisions of the muscular arteries (second-order, third-order, lobular, and arterial branches) (Table II). The pulmonary vasculature of each lung was then dissected, and selected microscopic sections were studied.

#### Results

*I. Acute sequelae of experimental pulmonary embolism*

*Thromboplastin, Warner-Chilcott Division, Morris Plains, N. J.
†Dionosil aqueous, Glaxo Laboratories, Ltd., Greenford, England.

*Sodium and meglumine diatrizoate, Winthrop Laboratories, New York, N. Y.
‡Liquaemin Sodium 10, Organon, West Orange, N. J.

*Table I. Time of follow up studies (hours)*

| | Experiment number | Control | Immediate | Hours after embolization | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | ½ | 1 | 2 | 3 | 4 | 6 | 8 | 24 |
| Plain clot | | | | | | | | | | | |
| | 1 | | x | | x | x | | | | | |
| | 2 | x | x | x | x | x | x | | | | |
| | 3 | x | x | x | | x | x | x | | | |
| | 4 | x | x | x | x | x | | | | | |
| | 5 | | x | x | x | x | | x | | | |
| | 6 | x | x | x | | x | x | | | | |
| Radiopaque clot | | | | | | | | | | | |
| | 7 | x | | | x | | | x | | | |
| | 8 | x | x | | x | x | | x | x | | |
| | 9 | | | | | | | x | | | |
| | 10 | x | x | | x | | x | x | | | |
| | 11 | x | x | | | x | | | x | x | |
| | 12 | | x | | x | | | | | | x |
| | 13 | x | x | | | x | | | | | |
| | 14 | x | | | x | | | | | | x |
| | 15 | x | x | | x | x | | x | | | |
| | 16 | x | x | | x | x | | x | | | x |
| | 17 | x | x | | | x | | | | | |
| | 18 | x | x | | | x | | | | | x |
| | 19 | x | x | | x | x | | | | | x |
| | 20 | x | x | | | x | | | | | x |
| | 21 | x | x | | | x | | | | | x |
| | 22 | x | | | | x | | | | | x |
| | 23 | x | | | | | | | | | x |

*Table II. Classification of pulmonary vasculature of the normal dog*

| | Recognition by premortem angiogram | Recognition by postmortem arteriogram |
|---|---|---|
| Elastic arteries (diameter > 1.0 mm.) | | |
| MPA, LPA, RPA | + | + |
| Lobar | + | + |
| First-order (segmental*) | + | + |
| Muscular arteries (diameter 0.1 to 1.0 mm.) | | |
| Second-order | + | + |
| Third-order | +/− | + |
| Lobular | 0 | + |
| Atrial | 0 | +/− |
| Arterioles (diameter 0.3 to 0.1 mm.) | 0 | 0 |

*See Fig. 2 for further identification of first-order arteries.

DOCUMENTATION OF PULMONARY EMBOLISM BY PLAIN CHEST X-RAY FILMS. In each of the 17 dogs embolized with radiopaque blood clot, the opaque clots were clearly seen on plain chest x-ray films taken immediately after embolization. In all 17 dogs emboli were present in both lungs and in most dogs emboli were visible in each lobe of the lungs. There were wide differences in the size of the emboli resulting from the injection of blood clot.

ANGIOGRAPHIC ABNORMALITIES ASSOCI




Fig. 1. A normal pulmonary vascular pattern is demonstrated in the control angiogram (*left*). The plain chest film taken minutes after embolization with 3 ml. of radiopaque blood clot (*middle panel*) identifies numerous emboli in both lung fields. The angiographic abnormalities resulting from the presence of these emboli are demonstrated in the angiogram taken minutes later (*right*). Note the cutoff of the left lower lobar artery with resultant oligemia, cutoff of first-order branches of the right lower lobar artery, and a missing first-order branch of the left apical lobar artery.

ATED WITH THE KNOWN PRESENCE OF EMBOLI IN THE PULMONARY VASCULATURE. The radiopaque emboli noted on the plain films taken immediately after embolization were almost uniformly associated with identifiable abnormalities on the angiograms taken minutes later (Fig. 1).

These angiographic abnormalities were identified by reference to the plain film showing the location of the radiopaque emboli and to the control angiograms taken before embolization. The angiographic abnormalities were the same for the two types of emboli, plain blood and radiopaque blood clot.

Four different angiographic abnormalities were found to be associated with the known presence of emboli in the pulmonary vasculature.

1. Discrete or hazy cutoffs of arteries (Figs. 1, 3, and 8). This was the most common acute angiographic abnormality found to be associated with pulmonary embolization in this study. The arteries most frequently cut off were the first-order (elastic) arteries and second-order (muscular) arteries. At least two first-order arteries were cut off in the angiogram taken immediately after embolization in each experiment.

Cutoffs were less frequent among the larger elastic arteries. Lobar arteries were cut off in 11 of the 23 experiments. There were no cutoffs of the main right or left pulmonary artery.

With constant reference to the control angiogram, the number of obstructed first-order arteries on the angiogram immediately after embolization was tabulated in each experiment. The vascular supply to the seven lobes of the normal dog lung consists of 18 such first-order arteries, as shown in Fig. 2. These first-order arteries supply regions of the dog lung that are analogous to the bronchopulmonary segments of the human lung. If a lobar artery was cut off, the number of first-order arteries that it supplied was counted as being cut off. The average number of obstructed first-order arteries in the 23 dogs was 6.4 (range 2 to 15). This implies obstruction of at least one third (6.4/18.0) of the pulmonary vasculature. The total degree of pulmonary vascular obstruction would also include the occlusion of smaller arteries supplied by first-order arteries that had remained patent.

2. Complete absence of an artery without a visible cutoff (Fig. 3). In some experiments, arteries were occluded near their origin in such a way that they failed to visualize, but a cutoff was not apparent. This type of angiographic abnormality, particularly when it affected smaller arter-

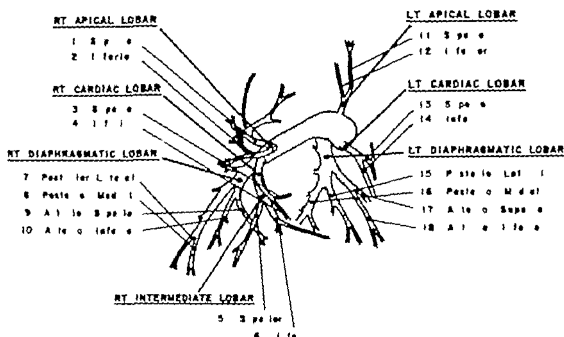



Fig. 2 Clas bcation of ascular upply t normal dog lung (7 lobar arteries 18 first order e sel ) Th chema of the pulmonary arterial tree of the dog in the right anterior oblique projection was de ed by one of u (H E ) on the ba of premortem angiograms correlated with postm ortem arteriograms and di section The nomen lature is an extension of that of Edw ard ad Brenner

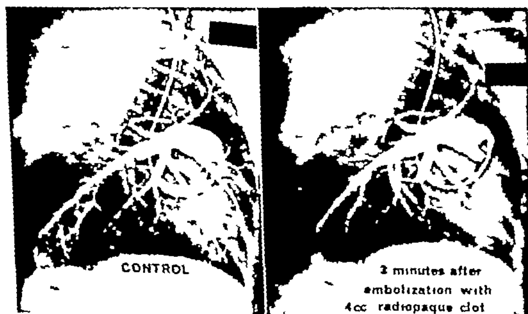



Fig. 3 I the o trol angiogram (*left*) th left cardiac lob artery with its two first-order branches w ll o lized d denoted by an arrow I the ngiogram taken 3 minutes fter e mbolizat n the ent re left card ac lobar artery absent yet point of cutoff cannot be detected in th art ry In the l ft l ower lobe three d wnstr ut ff of f rst-order arteries are present in the postembolization ngiogram




Fig 4 In the postembolization angiogram (right) a large intraluminal filling defect is present in the right lower lobe artery at point of bifurcation This is not present in the control angiogram (left)

ies could be detected only by reference to the control angiogram

3 Intraluminal filling defects (Fig 4) In dogs embolized with plain blood clot intraluminal filling defects that is negative shadows within the opacified pulmonary arterial tree were at times noted The subsequent postmortem studies established that the e intraluminal filing defects were due to the presence of emboli Intraluminal filling defects were best visualized in the oblique views and were most frequently noted at points of bifurcation

4 Areas of oligemia (Fig 5) In the postembolization angiogram in each experiment certain areas of the lung were found to be more radiolucent than the same area had appeared to be on the control angiogram In these radiolucent areas fewer small arterial branches were visualized than in the comparable area in the control angiogram In some cases these areas of oligemia were distal to lobar or first-order or second order arteries that were cut off In other cases oligemia occurred without other associated angiographic abnormalities and probably was caused by the obstruction of numerous vessels that were too small to be individually recognized by angiography These oligemic areas were most commonly seen in the lower lobes

ASSOCIATED HEMODYNAMIC EVIDENCE OF PULMONARY EMBOLIZATION In 21 of the 23 experiments embolization was accompanied by an increase in mean pulmonary arterial pressure of at least 5 mm Hg For the total group the mean pulmonary arterial pressure increased from an average value of 18 9 mm Hg in the control period to 30 3 mm Hg at 3 minutes after the release of emboli

EFFECT OF EMBOLIZATION ON SIZE OF MAIN PULMONARY ARTERIES Angiography provided no evidence of pulmonary vasoconstriction On the contrary detectable dilation of major pulmonary arteries almost always appeared on angiograms taken immediately after embolization The increase in diameter of the main pulmonary artery and its major branches is shown in Table III

*II Serial angiographic and hemodynamic changes after pulmonary embolism Results of follow up studies*

SERIAL CHANGES IN PLAIN FILM APPEAR

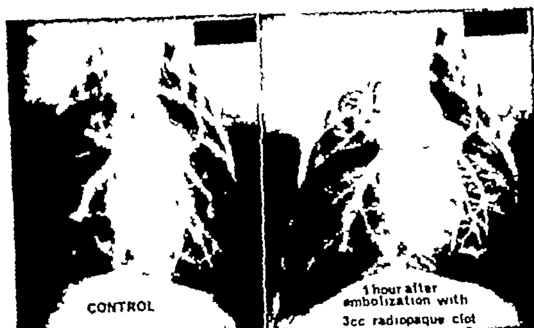



Fig 5 Comparison of the postembolization angiogram (*right*) with the control angiogram (*left*) indicates the presence of oligemic areas in both lower lobes in the postembolization angiogram In this experiment the areas of oligemia were associated with absent or cutoff first-order branches of the lower lobar arteries

*Table III Diameter (mm) of major pulmonary arteries before and immediately after embolization*

| Vessel | Before (Mean ± S E) | After (Mean ± S E) | t | p Value |
|---|---|---|---|---|
| PA | 22 1 ± 47 | 25 8 ± 58 | [illegible] | < 001 |
| LPA | 8 9 ± 23 | 10 8 ± 25 | 6 2 | < 001 |
| RPA | 11 1 ± 32 | [illegible] | 6 6 | < 001 |

[illegible]

SIZE OF RADIOPAQUE CLOT In the first 4 hours after embolization with radiopaque blood clot there were few changes in the radiographic size and location of the radiopaque clots Decreases in the size of the clots was noted in dogs restudied at 24 hours Fragmentation of the clot emboli as judged by the number of radiopaque emboli visible on the plain x-ray films did not occur after the immediate postembolization period

REGRESSION OF ANGIOGRAPHIC EVIDENCE OF EMBOLISM Each of the four types of angiographic abnormalities found to be associated with the presence of emboli in the pulmonary vasculature was reassessed in the follow up angiograms

The most readily detectable immediate angiographic evidence of embolization discrete or hazy cutoffs of arteries decreased with the passage of time Fig 6 (*top panel*) indicates the mean number of occluded arteries noted at each observation period The average number of occluded arteries progressively decreased from 6 4 immediately after embolization to 2 8 at 3 to 4 hours after embolization

The second type of angiographic abnormality the complete absence of an artery without detectable cutoff (see Fig 3) also

was quite transient The majority of these arteries reappeared during the first 4 hours after embolization

Oligemia as an angiographic manifestation of embolization was more persistent than cutoffs and absent arteries Significant decreases in oligemia did not occur during the first 4 hours of follow up However of 9 dogs restudied 24 hours after embolization oligemia was detectable in only 3

Filling defects as sequelae of pulmonary embolization demonstrated a different time course In most cases filling defects became more apparent with the passage of time On the immediate angiograms they frequently were subtle and could only be suspected whereas on later angiograms they became more apparent

SERIAL CHANGES IN HEMODYNAMIC SEQUELAE OF PULMONARY EMBOLIZATION The average mean pulmonary arterial pressure with respect to time after embolization is plotted in Fig 6 (*middle panel*) The pressure increased from a control level of 18 9 mm Hg to 30 3 mm Hg immediately after embolization and then decreased to 25 4 mm Hg at 1 hour after embolization with no significant change thereafter to 4 hours

SEQUENTIAL CHANGES IN SIZE OF MAJOR PULMONARY ARTERIES The average diameter of the main pulmonary artery is likewise shown in Fig 6 (*bottom panel*) The progressive return toward normal size after immediate dilatation is evident and correlates with the observed sequential changes in pulmonary arterial pressure

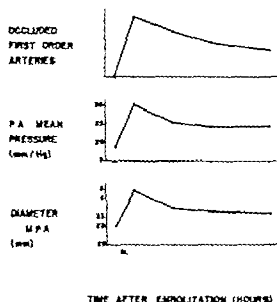



Fig 6 Changes after pulmonary embolization In these three panels the number of occluded first order arteries (*top panel*) average mean pulmonary arterial pressure (*middle panel*) and average diameter of the main pulmonary artery (*bottom panel*) are plotted for the control immediate postembolization and the 1 hour 2 hour and 3 to 4 hour post embolization studies The maximum number of occluded arteries and the maximum pulmonary arterial pressure and size were noted in the immediate postembolization studies (plotted at 0 hours) By 1 hour after embolization each of these three variables had shown significant returns toward their control values Additional minimal improvement occurred between 1 and 4 hours after embolization

*III Postmortem studies*

RESULTS OF RADIOGRAPHIC STUDIES The postmortem plain x ray films of the lungs were more sensitive in the detection of small radiopaque emboli than were premortem plain chest x ray films Radiopaque emboli present in vessels smaller than second order arteries could be detected only by the postmortem plain films of the excised lungs

Postmortem arteriograms reliably demonstrated abnormalities in association with radiopaque emboli visualized by postmortem plain films as illustrated in Fig 7 Abnormalities on postmortem arteriograms were most easily detected when emboli had caused complete arterial occlusion Complete embolic occlusion of even the smallest muscular arteries could be recognized Incomplete arterial occlusion was more difficult to identify by postmortem arteriography In these cases filling defects caused by the presence of partially occluding emboli were at times partially obscured by the presence of opaque injection medium surrounding the embolus

When the premortem angiographic findings were compared to the postmortem arteriographic findings excellent agreement was found except when emboli were present in arteries smaller than second order Just as radiopaque emboli could not be detected in these small arteries by premortem plain films abnormalities due to their presence could not be reliably detected by premortem angiography

In some cases partial embolic occlusion of an artery may be represented as apparent total occlusion by the single film tech

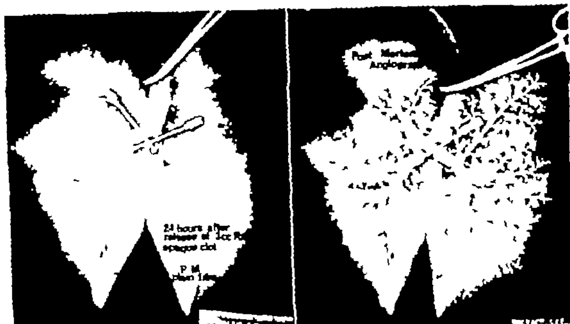



Fig. 7. In the postmortem plain film (*left*) numerous radiopaque emboli are present in first-order and second-order arteries, particularly at points of bifurcation. The postmortem arteriogram (*right*) demonstrates [illegible] filling of vessels distal to these embolic obstructions.




Fig. 8. In the premortem angiogram taken 4 hours after embolization (*left*) the left lower lobar artery [illegible] cut off just distal to the origin of the left cardiac lobar artery, and there is marked oligemia distal to the cutoff. In the postmortem arteriogram (*right*) the left lower lobar artery appears to be normal and there [illegible]. However, at the point marked by an arrow, a large partially occluding embolus [illegible] found [illegible] section.

nique of premortem pulmonary angiography. In Fig. 8 a cutoff in the left lower lobar artery with marked distal oligemia is present in the premortem angiogram (*left panel*). In the postmortem arteriogram (*right panel*) the left lower lobar artery is patent and there is no distal oligemia. A subtle filling defect is present in the postmortem arteriogram at the point at which the left lower lobar artery was cut off on the premortem angiogram. At dissection a large partially occluding embolus was found at this point in the artery.

RESULTS OF DISSECTION. No clots were found in the right ventricle or right atrium. The largest number of emboli were present in the lower lobes. Smaller numbers of emboli were found in one or more of the other lobes of the lung in each experiment. The arteries most frequently embolized in these experiments were the second order muscular arteries, particularly at points of bifurcation.

Of the 9 dogs that were sacrificed 24 hours after embolization, evidence of pulmonary infarction was found in only 1 dog.

In the 17 dogs embolized with radiopaque blood clot, Dionosil was found evenly distributed throughout each embolus. There was evidence of clot propogation in only 1 dog.

Abnormalities noted by premortem angiography were invariably associated with corresponding abnormalities in the pulmonary vasculature as found at dissection. There were no false positive findings by premortem angiography. However, false negative premortem angiographic findings occurred when emboli were present in arteries smaller than second order. Emboli in these small arteries were not recognized by premortem angiography unless they had resulted in detectable oligemia. All emboli found in second order and larger arteries at dissection were associated with abnormalities on the premortem angiograms.

## Discussion

The angiographic abnormalities found to be associated with the presence of thromboemboli in the pulmonary vasculature of dogs (cutoff of arteries, totally absent arteries, intraluminal filling defects, and areas of oligemia) are quite comparable to those reported in the clinical studies of Simon and Sasahara.[1] They also reported an additional angiographic abnormality, focal flow decrease, that is, a regional decrease in the rate of flow of contrast medium to one or more segments of the lung. This type of abnormality cannot be detected per se by the single film technique of angiography utilized in this study. However, as noted above (Fig. 8), in some cases large partially occluding emboli as noted at postmortem examination had appeared as complete cutoffs on the premortem angiograms taken by the single film technique. It is likely that in these cases the angiographic appearance of complete occlusion by the single film technique was a reflection of marked delay in the passage of contrast medium beyond the point of partial embolic occlusion. With the serial film technique of angiography, this same partial embolic occlusion might have been represented angiographically as delayed filling of the lung segment distal to the point of partial occlusion. The inability to study specifically the rate of flow of contrast medium to each part of the lungs is the greatest disadvantage of the single film technique of angiography. By the single film technique, delayed filling of a segment of the pulmonary vasculature can be detected only if it is a relatively marked delay. Similarly, asymmetrical prolongation of the arterial phase cannot be detected by the single film technique.

In the follow-up studies reported in this investigation, changes in the size and location of thromboemboli were determined by following the size and location of the radiopaque clots by plain chest x-ray films. The reliability of using the radiopacity of these clots as an index of their size has been established by Allison and associates,[8] who demonstrated in in vitro experiments that a decrease in the radiopacity of clots impregnated with Dionosil is not due to preferential washout of Dionosil. This was confirmed by our studies in which Dionosil was found to be evenly distributed throughout each radiopaque clot examined at postmortem.

Few significant changes were noted in the size or location of these radiopaque thromboemboli during the first 4 hours after embolization. However, by 24 hours the

radiographic size of the emboli had decreased by plain chest film These findings are in agreement with those of Allison and co workers[4] Browse and James[13] and Just Viera and Yeager[14]

In contrast to the paucity of observed changes in the size and location of radiopaque emboli during the early follow up studies significant angiographic changes were noted during this same early follow up period The number of obstructed arteries showed a sharp decrease (Fig 6) and arteries that had failed to visualize in the immediate postembolization angiograms reappeared Thus angiographic evidence of resolution of embolic obstruction of the pulmonary vasculature correlated well with the observed decreases in the mean pressure and diameter of the pulmonary artery over the same period of time (Fig 6)

Similar angiographic evidence of resolution of thromboembolism has been observed in man by Sautter[15] Simon and Sasahara[1] and Alexander and associates[7]

## Summary and conclusions

Comparison of selective pulmonary angiograms in two or more projections taken before and immediately after embolization of healthy dogs with known amounts of autologous blood clot indicated that four different angiographic abnormalities are associated with the presence of pulmonary thromboemboli Two abnormalities were recognized with relative ease intraluminal filling defects due to the presence of clot and discrete cutoffs of arteries The other two angiographic abnormalities areas of oligemia and total absence of arteries without a visible cutoff could most reliably be be detected by comparing the postembolization angiogram with the control angiogram

In follow up studies angiographic and hemodynamic evidence of resolution of thromboembolism (a sharp decrease in the number of obstructed vessels and a return of pulmonary arterial pressure and the size of the pulmonary artery toward normal values) was noted within 4 hours of embolization The angiographic and hemodynamic improvements observed during this early follow up period were far greater than the changes observed in the size and location of the thromboemboli over the same period of time

At postmortem the greatest number of emboli were found in the lower lobes especially at points of bifurcation in second order (muscular) arteries The postmortem findings were quite comparable to those in pulmonary embolic disease in man

The reliability of this technique of angiography in detecting pulmonary thromboemboli was assessed by comparing the premortem angiographic findings with the findings of postmortem arteriography and dissection There were no false positive findings by premortem angiography False negative angiographic findings frequently occurred when thromboemboli were located in arteries smaller than second order Embolization of these small arteries could be detected only if their obstruction had caused angiographic evidence of oligemia

The difficulty in detecting subtle angiographic changes without the use of control angiograms the uncertainties in the detection of embolization of small pulmonary arterial branches and the observed early angiographic improvement that occurred even though thromboemboli were still present in the pulmonary vasculature all suggest that pulmonary angiography in clinical studies may tend to underestimate rather than overestimate the abnormalities due to pulmonary thromboembolism

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# Case reports

## Electrocardiographic changes in lightning stroke

*C. D. Burda, M.D.*
*Shreveport, La.*

Lightning is a brief atmospheric discharge of highly damped electrical current with enormous energy.[1] Although its effects upon the human body are generally similar to those observed in household electrical and high voltage wire accidents, the local tissue burns and destruction are usually not so mutilating and severe. Also various neurological, ophthalmic, auditory, pulmonary, and psychiatric complications and sequelae are seemingly more common in survivors of lightning strokes. Sudden death is caused by paralysis of the respiratory center, ventricular fibrillation, cardiac arrest, or any combination of these events; however, survival after prolonged apnea with the aid of vigorous cardiac resuscitative and hypothermic measures has been reported.[2]

Electrocardiographic changes have rarely been reported in the victims of lightning stroke who were merely stunned or rendered temporarily unconscious. These findings have been patterns of myocardial infarction in three instances[3,4] and subepicardial injury and ischemic changes in one case.[4] There was no clinically evident cardiac dysfunction or sequelae. Arrhythmias such as atrial and ventricular fibrillation also may be seen in more severe cases.[4] Because of the rare opportunity to observe serial electrocardiographic changes in the lightning stroke phenomenon and the absence of such reports in the American and English literature, it was deemed to be worth while to make this case report and review of the literature.

### Case report

A 14-year-old Negro male caddy was struck unconscious on the golf course by a discharge of lightning while seeking shelter under a tree during a thundershower. Ten to 15 minutes elapsed before the golfers noticed that he was lying on the ground. At this time he was conscious, oriented, moved all extremities, and complained only of mild abdominal pain. There was no past history of heart disease or serious illnesses.

Positive physical findings $1\frac{1}{2}$ hours later at the time of admission to the hospital were limited to the skin and abdomen. First- and second-degree burns were found on the left scapula, the left flank, and left lateral thigh. The abdomen was slightly distended and diffusely tender with hypoactive bowel sounds. Blood pressure and pulse were normal; likewise, heart and lung examinations were unremarkable.

Abdominal x-ray films showed a mild adynamic ileus, whereas the chest film was within normal limits. Complete blood count showed a moderate leukocytosis with leftward shift in the differential. Urinalysis, blood urea nitrogen, blood sugar, and serum electrolytes were within normal limits. SGOT and SGPT values were 36 and 16 units, respectively (normal values 8-40 and 5-35 units). He was asymptomatic after 24 hours of treatment with nasogastric suction and intravenous fluid.

Representative electrocardiograms of a series taken over a subsequent period of 12 months are shown in Figs. 1 and 2. The first was taken approximately 36 hours after admission on Aug. 11, 1964, and revealed a normal sinus rhythm of 60 per minute, P-R interval of 0.14 sec., QRS duration of 0.08 sec., and a markedly prolonged Q-T interval of 0.56 to 0.62 sec. (Q-T of 0.33 sec.). The P waves were generally low and notched. The T waves were deeply inverted in Leads II, III, aVF, V, V, and upright

From the Department of Internal Medicine and Louisiana State University Postgraduate School of Medicine, Confederate Memorial Medical Center, Shreveport, La.
Received for publication Dec. 14, 1964.

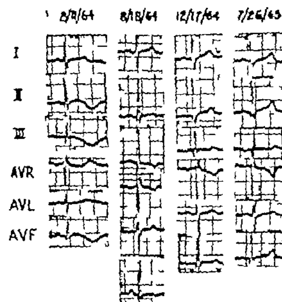



Fig. 1. Serial electrocardiographic changes in lightning stroke (standard limb and augmented leads).

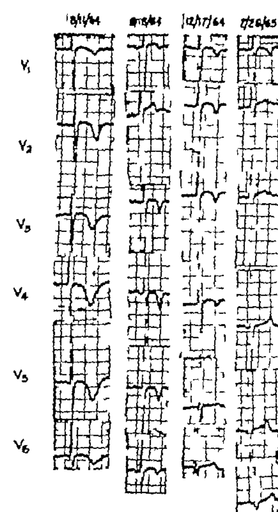



Fig. 2. Serial electrocardiographic changes in lightning stroke (precordial leads V₁-V₆; first half standardization on Aug. 11, 1964; V₁ at half standardization on Aug. 18, 1964).

in Lead ... The S-T segment were generally ... One week later (Aug. 18, 1964) there was slight ... shift in ... QRS amplitude and ... shortening of the Q-T interval. The ... were slightly more prominent and became diphasic in ... and $V_3$. The T wave inversions generally persisted except in Lead aVR and ... which ... became inverted and diphasic respectively. Approximately 4 months later (Dec. 17, 1964) the ... normal ... present ... Lead ... The improvement continued ... in the precordial lead resulting in a normal electrocardiogram approximately 12 months after the lightning stroke (July 26, 1965).

## Discussion

Terranova[3] observed resolution within 7 weeks of a posterior myocardial infarct-like pattern in a young male struck by lightning who suffered no cardiac sequelae. A similar abnormality was observed in a young female with tissue burns and neurological and psychiatric complications;[4] however, in this instance the duration of follow-up was only 6 weeks. Von Graf[6] also reported comparable electrocardiographic changes in a 30-year-old woman who had been struck by lightning in the left chest, abdomen, and inguinal areas. These changes began to resolve in 3 days and by the end of 3 months the electrocardiogram was normal. Electrocardiographic evidence of high anterior and diaphragmatic injury was recorded in a case of fatal cardiac arrest after restoration of the heartbeat by open cardiac massage.[7] These changes were thought to have been secondary to the massage. Five other young adults who had been involved in the same accident had no significant electrocardiographic changes.

Subepicardial ischemic and/or injury changes similar to those in the present case were noted by Schmidt[4] in one other victim of lightning injury. There was initial S-T segment elevation and T wave inversion in Leads II and III. During the

next 2 weeks marked T wave inversion occurred in the precordial leads and in Lead I. These changes were accompanied by prolongation of the Q-T interval and a striking axis shift. These abnormalities improved remarkably within 8 months and the electrocardiogram became normal within approximately 12 months. The development of the notched (Fig. 1, Aug 18, 1964), although not abnormally wide or tall, P waves and diphasic P in Leads $V_1$ and V (Fig. 2, Aug 18, 1964) in this case is interesting and might be taken as evidence for some atrial enlargement or injury.

A primary electrical injury or burn of the myocardium by the lightning is a reasonable explanation for the electrocardiographic changes observed in this and other such cases, since necropsy studies of a few cases have revealed epicardial hemorrhages[4] and a peculiar spiral malformation of the myocardial fibers.[5] In other instances[6,8] gross and microscopic myocardial abnormalities have been absent or insignificant. Similarly, in AC shock and countershock defibrillation experiments on dogs, evidence of fibrinous epicarditis, subepicardial venous thrombosis and muscle fiber necrosis has been found.[1] Such changes are known to produce subepicardial ischemic T wave changes and vectors.[11] Also patterns similar to myocardial infarction, T wave inversions, atrial and ventricular fibrillation and ventricular tachycardia have been experimentally produced in animals with electric currents.[13]

The interpretation of patterns of infarction in cases of lightning stroke as being synonymous with coronary occlusion should be viewed with caution since it is known that various other conditions without coronary thrombosis, such as pericarditis, myocarditis, cerebrovascular disease,[1] pulmonary embolism, pancreatitis, electrolyte imbalance and ventricular hypertrophy, among others, may produce identical electrocardiographic changes.[1] Primary myocardial damage from the lightning without coronary involvement is a more likely explanation for these electrocardiographic patterns, although the precipitation of a true myocardial infarction by the stress and trauma of the lightning bolt in an older patient with coronary artery disease could conceivably occur.

It has been postulated that the discharge of lightning simultaneously causes arrest of the respiratory center, violent ventricular systolic contraction and shock. This is followed by slow ventricular relaxation and resumption of the cardiac beat; however, the apnea and resulting anoxia induce a secondary cardiac arrest which then leads to death. Severe and unpredictable electrocardiographic abnormalities might thus result from either myocardial anoxia or possibly from stimulation of the central nervous system via sympathetic storms.[14] Finally, no gross derangement in serum electrolytes was found in this case, which would exclude an electrolyte imbalance as a cause of these electrocardiographic changes.

**Summary**

Serial electrocardiographic changes in a 14 year old Negro male who had been rendered temporarily unconscious by a stroke of lightning are presented. Deep symmetrical T wave inversion in Leads II, III, aVF, $V_1$-$V_4$, with prolongation of the Q-T interval, were interpreted as being compatible with diffuse myocardial injury. These changes resolved in approximately 12 months and no immediate or long term adverse effect upon the heart was clinically evident.

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# Aneurysm of ventricular septum with outflow obstruction of the venous ventricle in corrected transposition of great vessels

*Charles P Summerall III M D **
*George H A Clowes Jr M D **
*John A Boone M D ****
*Charleston S C*

Complex or uncommon congenital mal formations of the heart remain a challenge in diagnosis and in corrective surgery Only recently have there been re ports of the recognition and successful cor rection of outflow obstruction in the right ventricle due to an aneurysm of the mem branous portion of the ventricular sep tum[1,2] The following ca e represents an unusual association of this lesion with cor rected transposition of the great vessels and subvalvular pulmonic stenosis

## Case report

A 2 year-old white housewife (MCH 52507) en tered the Medical Coll ge Ho pital on J n 20 1965 for card ac surgery

In 1950 t the age of 8 y ars the pat ent had undergone cardiac evaluation because of a heart murmur first disco ere l prior to tonsillectomy when she was 4 ye rs old Her b rth and infancy had been unc entf l her growth had been normal and she had had no ignifica t symptoms One of her three sist r had small defect of the entricular sep tum confirmed by cardiac catheterization On phy ical examinat on the blood pressure was 110/70 m Hg There was no cy nosis The second hea t sou d was loud t in the pulmonic are There w a l u l st olic murm l g the l ft sternal border mo t intense in the third ntercostal pace with an overlying thrill An electrocardiogram showed hy pertrophy of the right entricle (Fig 1) Cardiac fluoroscopy suggested a entricular septal defect Catheterization of the right side of the heart re ealed an increase n oxygen saturation from level of 69 per cent low in the right entricle to 88 per ent in the outflow tract The pressure in the right ventricle wa 100/0 mm Hg The tip of the catheter apparently passed through a ventricular septal de fect into the aorta where the oxygen saturation wa 97 per cent and the pressure 100/70 mm Hg The pulmonary artery could not be entered

Sub equently the patient lived an ntv normal lif with no symptoms other than m ld fatigability In 1967 t the age of 20 years she had n unevent l pregnancy In 1964 n part because of increasing fatigability and occasional brief episodes of weak ness he again underwent car iac ev luation Phy cal examination re ealed systolic murmur long the left sternal border w th relati e prominence of the cond heart sound in the pulmonic area An electrocardiogram showed hypertrophy of the right entricle that was somewhat more marked than on previous tracings (Fig 1) Card ac fluo osc py w with n normal lim ts Cardia catheterization re ealed a pre sure of 100/0 mm Hg in the right en tricle w th no evidence from xygen saturation data of a left to ight shunt i th chamber The pul mon ry artery could not be entered The theter crossed mall tr l septal defect nd entered the left entricle where the pressure wa 90/0 mm Hg

F m the Departm of Med c d Surgery Med l C ll Hosp l Med cal Coll of South Car l na Ch les ton S C

Recei ed for publicat on Dec 22 1964

Associ t Medicine Address Department of Med cine Med cal C llege Hospit l Med al College of So h Ca o lina 55 Do ghty St Ch lest S C
**Professor of rgery Prese ddr ss H rva d Medical School Bost M ss
***Professor of Med ne

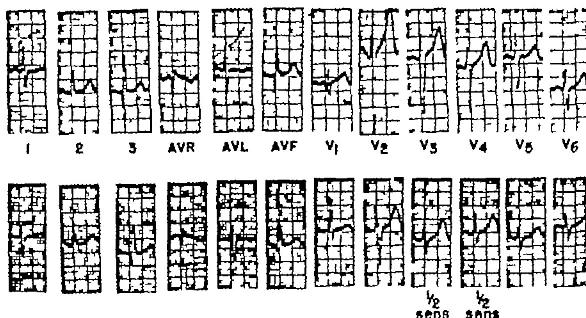



Fig. 1. Standard electrocardiograms show hypertrophy of the right ventricle when the patient was 8 years old (tracings a, 1, 2 recorded on Oct. 5, 1950) and more advanced hypertrophy when she was 22 years old (tracings at bottom recorded on Dec. 8, 1964).

nd the oxygen saturation was 98 per cent. Left ventriculography (Fig. 2) demonstrated a prominent bulge in the upper portion of the septum in close relationship to the aortic valve. Right ventriculography (Fig. 3) showed a large filling defect in the outflow tract close to the pulmonary valve which was unusually low in position. The septal contour of the ventricle was smooth.

On Jan. 21, 1965, the patient underwent cardiac exploration via median sternotomy with the use of cardiopulmonary bypass. The aorta and pulmonary artery were transposed. Right atriotomy disclosed a small atrial septal defect. The atrioventricular valve appeared to be normal. A pulmonary arteriotomy permitted exploration of the right ventricle, which contained a large aneurysm of the ventricular septum. During systole the aneurysm protruded into the outflow tract. It apparently produced a complete obstruction until the pressure in the right ventricle reached systemic level and partially emptied the aneurysmal sac to open a route for flow into the pulmonary artery. The aneurysm arose from a fibrous ring about 1 cm. in diameter. There was no actual communication between the ventricles. The edges of the ring were closed with interrupted mattress sutures with inversion of the aneurysmal sac into the left ventricle without perforating it. There was also a subvalvular stenosis caused by a thickened band of fibrous tissue which was partially excised. After thoracotomy, prior to the repair, the pressure in the right ventricle was 85/0 mm. Hg and the pressure in the pulmonary artery was 13/5 mm. Hg. After the repair the corresponding pressures were 35/0 and 10/0 mm. Hg. The patient had an uncomplicated convalescence and returned to full activity with relief of the previous fatigability. A moderately loud systolic murmur persisted. On May 15, 1965, she again underwent right heart catheterization. The pressure in the right ventricle was 62/0 mm. Hg and the systemic arterial pressure 90/70 mm. Hg. Cineangiocardiography demonstrated a residual subvalvular pulmonic stenosis. No trace remained of the aneurysm of the ventricular septum.

## Discussion

Aneurysms of the membranous portion of the ventricular septum constitute an unusual group of lesions that seldom have permitted accurate diagnosis during life. In an analysis of the anatomic and roentgenographic features of these defects, Baron and associates[3] described several cases diagnosed by left ventriculography and they emphasized that wide spread use of this technique would undoubtedly identify similar lesions with increasing frequency in a variety of clinical circumstances. Steinberg[4] reported the angiocardiographic demonstration of a septal aneurysm in a 60 year old woman whom he studied in 1950, in all probability the earliest such diagnosis in a living patient. Two additional cases reported by Lebach[5] and by Campbell and co-workers were

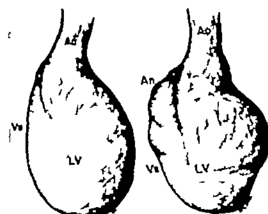



Fig 2 Artist's drawing of one left ventriculogram in diastole (*left*) and in systole (*right*) During systole the aneurysm (An) forms a prominent bulge in the upper portion of the ventricular septum (Vs) immediately inferior to the aortic root (Ao)



Fig 3 Selective right ventriculogram obtained in 1964 in the right anterior oblique projection A prominent filling defect is present in the ventricular outflow tract The ventricular contour is triangular

diagnosed by angiocardiography in essentially asymptomatic young women with loud systolic murmurs In neither case was an intracardiac shunt detected Schumaker and Glover[7] studied a 6-year old patient with the clinical and catheterization findings of a small ventricular septal defect Left ventriculography revealed a septal aneurysm which they corrected surgically It arose from a base 12 mm in diameter and contained a 3 mm interventricular communication Perasalo and associates reported their findings in a 27 year old woman in whom the catheterization data indicated a large left to-right shunt at the ventricular level and a systolic pressure gradient of 50 mm Hg in the right ventricular outflow tract At operation they found an aneurysm 4 cm in length and 3 cm in diameter which protruded into the right ventricle below the crista supraventricularis and partially obstructed the infundibulum This aneurysm contained a 1 cm interventricular communication Das Jahnke and Walker[4] reported a similar lesion in a 12 year old girl in whom the catheterization data had shown a moderate left to-right shunt at the ventricular level and a systolic gradient of 20 mm Hg in the outflow tract

Our patient presented two unusual and closely related features She had corrected transposition of the great vessels and a marked degree of obstruction of the outflow tract of the venous ventricle with a systolic gradient of 50 mm Hg measured at operation Angiocardiographic studies had suggested the positional transposition of the aorta and the pulmonary artery as confirmed at surgery and there was obvious functional correction Other roentgenographic features conformed to the criteria suggested by Ellis and co-workers[8] for the diagnosis of corrected transposition (1) proximity of the pulmonary valve to the right atrioventricular valve without interposition of a crista supraventricularis or infundibulum and (2) smooth internal contour of the venous ventricle At operation the base of the aneurysm of the membranous septum was close to the pulmonary valve which permitted exposure and repair through a pulmonary arteriotomy Examination of the right atrioventricular valve at operation revealed no distinct abnormality although postoperative angiocardiograms suggested that this valve was in fact bicuspid and structurally similar to a normal mitral valve

The anatomic relationships of the membranous portion of the ventricular septum

in corrected transposition of the great vessels clearly predisposed to the high degree of obstruction of the outflow tract that was observed in this patient. In a normal heart, the membranous septum lies close to the aortic valve, with its interventricular component placed immediately below the right coronary aortic cusp. In the right ventricle, the membranous portion of the septum lies below the crista supraventricularis, and an aneurysm projecting at this site into the lumen of the ventricle will not cause serious obstruction unless it reaches considerable size. With inversion of the ventricles, however, these relationships are reversed. The crista supraventricularis lies in the arterial ventricle. The outflow tract of the venous ventricle is short, and an aneurysm arising in the membranous septum will project into the outflow tract immediately below the pulmonary valve. Some degree of obstruction of the outflow tract is inevitable.

The specific pathogenesis of aneurysms of the membranous portion of the ventricular septum is controversial. Lev and Saphir[9] in an extensive review of this anomaly, agreed with a theory proposed by Mall in 1912, who postulated that the membranous septum, lying somewhat tangential to the root of the aorta, could be structurally weakened by a minor degree of rightward displacement of the bulbar septum. After birth, high pressures in the left ventricle would then progressively distend the aneurysmal sac. In support of a close relationship between abnormalities of the aortic root and aneurysms of the membranous septum, these authors cited from the literature 3 cases of aneurysms in both the membranous septum and in the sinus of Valsalva, and 6 cases of aneurysms involving the aorta and the membranous septum in continuity. They discussed, however, the alternative possibilities that aneurysms of the membranous septum might result from (1) defective formation of the endocardial cushions or (2) isolated defective fusion of the proximal bulbar swellings. Baron and associates[3] in evaluating Mall's theory, could find no evidence of an abnormality of the aortic root in their clinical series or in 2 autopsy cases of septal aneurysms. The occurrence of such aneurysms in patients with corrected transposition of the great vessels, as in this case and in an autopsy case mentioned by Baron,[3] is also somewhat at variance with Mall's theory, for with ventricular inversion the membranous septum loses its close relationship to the aortic root. These considerations tend to implicate a defect in the complex fusion of the muscular septum, the endocardial cushions, and the conus ridges rather than a displacement of the bulbar septum, as the principal feature in the pathogenesis of congenital septal aneurysms.

An additional feature of this case was the presence of subvalvular pulmonic stenosis. The obstruction may well have resulted from a flap of accessory valve tissue arising from the pulmonary and atrioventricular valves, comparable to the lesions described by Levy and co-authors[11] in 3 cases of corrected transposition of the great vessels. Such a lesion would explain the difficulty encountered during heart catheterization in advancing the tip of the catheter into the pulmonary artery. Isolated subvalvular stenosis was not encountered in 33 cases of corrected transposition of the great vessels reviewed by Schiebler and associates,[18] although pulmonic valvular or combined valvular and subvalvular stenosis was present in 6 of these cases.

A further aspect of this case is the apparent late spontaneous closure of a defect of the ventricular septum initially demonstrated by heart catheterization when the patient was 8 years old. Although the significance at that time of the oxygen saturation data, which suggested a bidirectional shunt at the ventricular level, is open to question, the pressure data clearly demonstrated that the catheter passed through the ventricular septum into the aorta. Fourteen years later, there was no evidence of such a defect by angiocardiography or at surgical exploration.

## Summary

This report describes a patient with corrected transposition of the great vessels and with an aneurysm of the membranous portion of the ventricular septum, which was surgically repaired. The aneurysm caused obstruction of the outflow tract of the venous ventricle, a hemodynamic com

plication that is essentially inevitable when an aneurysm of significant size develops in the presence of ventricular inversion Subvalvular pulmonic stenosis was also present

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# Clinical pathologic conference

*James H. Moller, M.D.*
*George R. Noren, M.D.*
*Paul R. David, M.D.*
*Kurt Amplatz, M.D.*
*Vladimir I. Kanjuk, M.D.*
*Jesse E. Edwards, M.D.**
*Minneapolis and St. Paul, Minn.*

DR. MOLLER. This 6 month old infant was the product of the third pregnancy of a 29 year old mother. The child was delivered after 38 weeks of gestation, and the birth weight was 4 pounds and 15 ounces. The infant did not cry at birth and during his first 24 hours of life the mother was told that the child had congenital cardiac disease. The patient gained weight during the first 6 months of life and was generally asymptomatic until 3 days prior to admission, when he became lethargic and pale and experienced difficulty in breathing. On admission to the University of Minnesota Hospitals he presented as a pale, irritable infant. The pulse rate was 165 per minute and the respiratory rate was 48 per minute. The lungs were clear. No murmur was present but the pulmonary component of the second cardiac sound was accentuated. The hemoglobin concentration in the blood and the leukocyte blood count were normal.

The electrocardiogram (Fig. 1) revealed signs of right atrial enlargement and of marked right ventricular hypertrophy. The thoracic roentgenogram showed enlargement of the right side of the heart with a normal sized left atrium (Fig. 2). The pulmonary fields showed a pattern of pulmonary venous obstruction. The infant was digitalized and placed in a croup tent.

During the period of hospitalization the infant manifested recurrent episodes of acute pulmonary edema, each characterized by marked dyspnea, pallor, and the presence of pulmonary râles. These attacks were treated with morphine sulfate and phlebotomy, and during one such episode, 2 weeks after admission, the infant died.

During the infant's life a venous angiocardiogram had been recorded. This demonstrated no right to left shunt at either the atrial or ventricular levels. The circulation through the pulmonary circuit was very slow, and the pulmonary veins were not delineated, although a small amount of contrast material was seen to enter the left atrium. Dr. Noren will describe the catheterization findings.

DR. NOREN. Cardiac catheterization was performed twice (Table I). These studies demonstrated pulmonary arterial hypertension with an elevated pulmonary arterial wedge pressure. Three pulmonary veins were catheterized from the left atrium, and in each the pulmonary venous

From the Departments of Pediatrics, R[illegible] [illegible] Pathology, [illegible] of Minnesota, Minneapolis, Minn., and [illegible] Department of Pathology, The Charles T. Miller Hospital, St. Paul, Minn.
This [illegible] was supported by Public Health Service Research Grant # RO1 HE 08494 and Research Training Grant # T1 HE 5370 from the National Heart Institute.
Received for publication May 9, 1966.
*Address: Department of Pathology, The Charles T. Miller Hospital, 125 W. College Ave., St. Paul, Minn. 55102.

*Table I. Synopsis of data obtained at each cardiac catheterization*

| Site | First catheterization | | Second catheterization |
|---|---|---|---|
| | Oxygen saturation (per cent) | Pressure (mm Hg) | Pressure (mm Hg) |
| Superior vena cava | 30 | — | — |
| Inferior vena cava | 30 | — | — |
| Right atrium | 30 | 8/2 2 | 12/7 8 |
| Right ventricle | 30 | 75/0 12 | 100/0 |
| Pulmonary artery | 30 | 75/35 $\overline{50}$ | 100/40 50 |
| Pulmonary arterial wedge | — | 37/13 $\overline{20}$ | 37/15 $\overline{30}$ |
| Pulmonary vein | 85 | 27/17 $\overline{23}$ | — |
| Left atrium | 83 | 22/10 | 17/5 $\overline{12\ 5}$ |

pressure was higher than the left atrial pressure.

At the time of the first catheterization a selective pulmonary arteriogram was recorded which revealed slow circulation through the pulmonary circuit. The pulmonary veins were not clearly delineated. The left atrium was demonstrated to be of normal size. At the time of the second cardiac catheterization a left atriogram was obtained. This demonstrated that the left atrium and left ventricle were each of normal size. There was no reflux of contrast material into the pulmonary veins.

DR. MOLLER. Dr. David, would you discuss the differential diagnosis?

DR. DAVID. This 6-month old infant exhibited manifestations of cardiopulmonary disease. Initially, when a physician sees an infant with tachypnea and tachycardia but without a cardiac murmur, he strongly considers pulmonary disease.

The increased anteroposterior diameter of the thoracic cage, electrocardiographic signs of marked right ventricular hypertrophy, and the auscultatory findings of pulmonary hypertension exhibited by this infant could be manifestations either of severe chronic acquired or congenital pulmonary disease or of a cardiovascular malformation. The degree of right ventricular hypertrophy indicated by the electrocardiogram would appear to be unusual for chronic pulmonary disease at this age, particularly in view of the lack of pulmonary symptoms during the major portion of the infant's life.

The thoracic roentgenograms may give us an impression of whether pulmonary disease is present. May we see these please, Dr. Amplatz.

DR. AMPLATZ. In this age group it is of course very difficult to differentiate between increased pulmonary vascularity and pulmonary disease. As may be seen, however (Fig. 2), the pulmonary densities are so diffuse and the heart so definitely enlarged that we would very strongly consider pulmonary edema rather than parenchymal disease of the lungs. If pulmonary disease is present, it may be in the form of pulmonary hemosiderosis secondary to venous obstruction. The roentgenogram in fact is demonstrative of the latter condition.

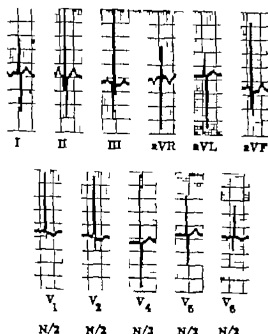



Fig. 1. The electrocardiogram.



Fig. 2. Anteroposterior thoracic roentgenogram. Moderate cardiomegaly is present. A diffuse granular appearance is evident in the pulmonary fields.

DR. DAVID: We agree with the interpretation of Dr. Amplatz that there is no evidence of pulmonary parenchymal disease and we will focus attention on the cardiovascular system. The elevated pulmonary arterial wedge pressure confirms the presence of a cardiac lesion on the left side. The diffuse venous congestion or so-called ground-glass appearance of the pulmonary fields demonstrated in the thoracic roentgenogram is suggestive of pulmonary venous obstruction. These features represent the foundation upon which to build a differential diagnosis.

Several cardiovascular malformations are associated with the roentgenographic picture of pulmonary venous obstruction. Lucas and associates[1] reviewed the problem of pulmonary venous obstruction in the pediatric age group and on the basis of the electrocardiogram divided cases of pulmonary venous obstruction into two groups: (1) those with signs of right ventricular hypertrophy and (2) those with signs of biventricular hypertrophy. The former group was considered to be indicative of obstruction to pulmonary venous return located at or proximal to the mitral valve, whereas in the latter group the lesion is located distal to the mitral valve, as in aortic stenosis, coarctation of the aorta, and other lesions causing left ventricular hypertrophy.

This broad approach is applicable in our case. One must recognize, however, that certain conditions distal to the mitral valve may give electrocardiographic signs of only right ventricular hypertrophy. Such conditions include endocardial fibroelastosis with hypoplasia of the left ventricle and hypoplastic left ventricle with atresia or stenosis of the aortic valve. Each of these conditions was excluded by the angiocardiographic findings of a normal-sized left ventricle. On the basis of the roentgenographic and electrocardiographic evidence of right ventricular hypertrophy, we know that the obstructive anomaly is at or proximal to the level of the mitral valve, and several diagnostic possibilities exist.

One of these is total anomalous pulmonary venous connection with obstruction to the pulmonary venous return, but several features exclude this condition. The catheterization data and angiographic features indicate no hemodynamically significant septal defects. A pressure difference of 14 mm. Hg exists between the right atrium and the left atrium, which is important evidence against the presence of an atrial septal defect. No arterialization was present in the chambers on the right side or in the venous vessels. A venous angiogram failed to demonstrate a right-to-left shunt.

Congenital mitral stenosis should be considered in the differential diagnosis, but this malformation is usually accompanied by a cardiac murmur. The absence of radiologic and electrocardiographic evidence of left atrial enlargement does not eliminate this possibility, since the left atrium is not necessarily enlarged in this condition in infancy. The normal left atrial pressure in the presence of an intact atrial septum eliminates consideration of any other significant obstructive lesions, such as supravalvular stenosing ring, at the level of the mitral valve.

The reported left atrial pressures are confusing. The pressure recorded during the first catheterization was elevated, but during the second cardiac catheterization the values were considered to be normal. I think that in such cases the wave form or shape of the pressure curve may be decisive in the interpretation. Normally the v wave is predominant



Fig. 3 Left atrial angiogram a Anteroposterior projection without reflux of contrast material into pulmonary vei ... orta are of no mal size b Lateral projection D nsely opacified left atrium No obstruction at mitral valve Left entricle and

in the left atrium A predominant a wave which was present in this case would favor either mitral steno is or lack of compliance of the left ventricle (in this case a hypoplastic left ventricle) Dr Noren was there anything significant about the left atrial pulse pressure curve?

DR NOREN The left atrial pressure re vealed an elevated a wave as recorded with the tip of the catheter positioned in the left atrial appendage It is known that pressures recorded at this site will exhibit falsely elevated a waves The left atrial pressures obtained during the second catheterization were measured at a site above the mitral valve

DR DAVID Now may we see the left atrial angiogram

DR AMPLATZ The left atriogram shows a normal sized very densely opacified chamber (Fig 3) Emptying is perhaps slightly slower than normal and in keeping with a small cardiac output The mitral valvular area is not remarkable angiographically There is no regurgitation of contrast material into the pulmonary veins a phe nomenon which is commonly seen in left atriograms The left atrium is well opacified the significance of this finding how ever is not certain

DR DAVID The left atrium shows no hold up of contrast material and this finding is further evidence against either mitral stenosis or stenosing supravalvular ring The data from each catheterization study indicate a pressure gradient between the level of the pulmonary capillaries and the left atrium The gradient was 10 mm Hg at the time of the first catheterization and 20 mm during the second study This evidence suggests that the obstructive lesion lies between the pulmonary capillary bed and the left atrium

Three types of obstructive lesions may be encountered at the junction of the pul monary veins with the left atrium These are cor triatriatum stenosis of individual pulmonary veins and hypoplasia of the common pulmonary vein

In adults cor triatriatum is commonly accompanied by a cardiac murmur whereas in only 50 per cent of children and infants is one present The angiographic studies have demonstrated a normal size and a normal shape of the left atrium which is contrary to the case in cor triatriatum The classic angiographic picture is one of a reduced distal atrial chamber with a flat or cut-off superior partition

In addition in our patient the tip of the catheter was directed into three of the pulmonary vein from the left atrium

phenomenon that would be unusual in the classic case of cor triatriatum. It is possible, however, that the pulmonary veins were catheterized through a hypoplastic common pulmonary vein. For this reason the fact that the pressure was higher in the pulmonary veins than in the left atrium does not aid in differentiating between the cor triatriatum and stenosis of individual pulmonary veins. In addition, the elevation of pulmonary venous pressure may be a reflection of the pulmonary arterial pressure, and in my opinion this finding is of no diagnostic value. The pulmonary angiogram may be most useful in delineating the pulmonary venous system. Dr. Amplatz, did the pulmonary arteriogram in this case delineate the pulmonary venous system?

DR. AMPLATZ: In this case the delineation of pulmonary veins was so poor that anatomic information was not obtained. On the other hand, the fact that the left atrium opacified even faintly was most useful in excluding the possibility of total anomalous pulmonary venous drainage with obstruction.

DR. DAVID: With the angiographic findings I would favor the diagnosis of stenosis of the individual pulmonary veins for three reasons. First, there was lack of visualization of a third atrial chamber, as would be apparent in cor triatriatum. Second, the poor delineation of the pulmonary veins would be expected in stenosis of the individual pulmonary veins. Third, the fact that the tip of the catheter could be directed into three of the pulmonary veins would be most unusual in a case of classic cor triatriatum. Therefore, my diagnosis is stenosis of the individual pulmonary veins.

DR. MOLLER: Dr. Kanjuh will present the necropsy findings.

DR. KANJUH: Each of the pulmonary veins joined the left atrium at normal sites (Fig. 4). The left lower, right upper, and right lower pulmonary veins were hypoplastic over the major portions of their respective courses, yielding an orifice of only about 1 mm. in diameter for each vein. The left upper pulmonary vein appeared to be normal, having an orifice of 5 mm. in diameter. Although no localized gross constrictive lesions were identified




Fig. 4. The left side of the heart and the pulmonary veins. The lungs have been turned so that the apices of the upper lobes appear at the lower portion of the illustration. The right upper and lower pulmonary veins (R.U. and R.L.) and the left lower (L.L.) pulmonary vein are hypoplastic. The left upper pulmonary vein (L.U.) is of normal size. The left atrium and the mitral valve are not remarkable.

in the pulmonary veins, each of the hypoplastic veins showed focal intimal thickening, mainly with fibrous tissue but also with smooth muscle in some areas (Fig. 5). The basic structure of the heart was normal, but right ventricular hypertrophy was a marked feature (Fig. 6). The foramen ovale showed characteristics of valvular competent patency. No ventricular septal defect was present. The ductus arteriosus was closed. An anomalous origin of the right subclavian artery from the aorta was identified. The exterior of the lungs was characterized by evidence of prominent visceral pleural lymphatics, and there was marked edema. The basic color of the pulmonary tissue was tan, suggesting hemosiderosis. The histologic appearance of the lungs was characterized by prominence and engorgement of the alveolar capillaries. Medial hypertrophy of the small muscular arteries was prominent, and muscularization of arterioles was a striking feature. Pleural and parenchymal lymphatics were wide. The pulmonary veins




Fig. 5. Photomicrographs of pulmonary veins. a, Left lower pulmonary vein shows focal intimal thickening. Elastic tissue stain. ×40. b, Left upper pulmonary vein structure is normal. Elastic tissue stain. ×10. c, Right lower pulmonary vein shows focal intimal thickening. Elastic tissue stain. ×40. d, Right upper pulmonary vein, pad of fibrous intimal thickening. Elastic tissue stain. ×110.



Fig 6 Right ventricle Prominent right ventricular hypertrophy The ventricular septum is intact

showed varying degrees of medial hypertrophy No distinctive differences could be identified in histologic structure between those lobes in which the pulmonary veins were hypoplastic and the upper lobe of the left lung in which the pulmonary vein was normal

DR MOLLER Dr Edwards would you please give a closing summary

DR EDWARDS The pathologic findings of severe degrees of pulmonary stenosis involving three of the four pulmonary veins is in keeping with the clinical features

Stenotic lesions of the pulmonary veins may be divided into two major groups as follows (a) those occurring in pulmonary veins that join the left atrium and (b) those in channels which are anomalously terminating veins[2] Stenosis of anomalously terminating pulmonary veins may result from (a) hypoplasia of such veins[3] (b) focal fibrous lesions of the intima[4] and (c) compression of veins by contiguous structures One example of the latter process occurs in that condition in which there is total anomalous pulmonary venous connection to a vein of the portal system Such veins pass through the esophageal hiatus of the diaphragm in company with the esophagus Obstruction to the pulmonary venous system may occur when food passes down the esophagus[3]

A second situation in which an anomalous pulmonary vein is obstructed occurs in those instances of total anomalous pulmonary venous connection to the left innominate veins in which the anomalous vein ascends between the left pulmonary artery and left main bronchus[1,5]

Let us return to the condition represented by the case herein presented that in which stenotic lesions occur in pulmonary veins which connect with the left atrium a condition which has been termed stenosis of individual pulmonary veins This condition may involve only one several or each of the pulmonary veins The lesions may appear either alone or in association with a variety of cardiac malformations

Among the relatively small number of reported cases of stenosis of each of the pulmonary veins an atrial septal defect has been associated in a few[7,8] The case presented in this conference is rare in that no cardiac malformation was associated with the pulmonary venous lesions The stenotic lesions usually are rather sharply localized to the veno-left atrial junction the stenosis being caused by intimal fibrous hyperplasia In such cases there is a potential for surgical correction A contrasting situation is presented by this case in that in addition to intimal lesions the disease in the pulmonary veins was characterized by long segments of hypoplasia

Of interest in the case presented is the fact that no histologic differences could be identified between the pulmonary lobe from which the veins were obstructed and the lobe without stenosis of its vein The probable explanation for this is that most of the blood circulating through the lungs must have passed through the upper lobe of the left lung The volume of blood passing through the anatomically left upper pulmonary vein must have exceeded its anticipated capacity so that this vein was functionally stenotic to the volume of blood entering it

*Diagnosis* Congenital stenosis of individual pulmonary veins without intracardiac anomalies

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# Emotional and sensory stress factors in myocardial pathology

## Neurogenic and hormonal mechanisms in pathogenesis, therapy and prevention

W. Raab, M.D., F.A.C.C.*
Burlington, Vt.

The approach to the controversial problem of emotional factors in the pathogenesis and preventability of degenerative heart disease is handicapped by several interacting difficulties: the complexity of mechanisms involved, semantic ambiguities, and the lack of coordination of masses of largely unutilized information incoherently scattered throughout the world literature.

In the following an attempt will be made to cope in this particular field with the growing demand for general broader knowledge integration through comprehensive reviews of the literature.[1,2]

In recent years several conferences were devoted to certain aspects of psychogenic cardiovascular regulation and pathology.[3-6] However, none of them concentrated on the emotion-related physiological and biochemical phenomena under discussion with regard to their direct interference in the metabolism and structure of the heart muscle. Yet these very interferences are of primary significance for the problem of degenerative heart disease. This was explicitly acknowledged by the Second National Conference on Cardiovascular Diseases in Washington in 1964. Its official summary emphasizes that the pathogenic role of psychological and higher nervous functions has received far less attention than their importance deserves, and that studies in this direction should be given a new public face and unusually long-term support.[7]

### I. Scope of the problem complex

The heart muscle itself and those of its functional, metabolic and structural qualities which are affected by influences from the central nervous system constitute the main object of numerous studies focused on the problem complex of degenerative (so-called coronary or ischemic) heart disease. Autonomic nervous, neurohormonal and endocrine mechanisms represent under sensory and emotional stress conditions the mediators of pathogenic modifications of cardiac metabolism. Socioeconomic, environmental and other emotional factors provide an important part of the ultimate background for cardiac degenerative changes and death.

It should be pointed out, however, that

From the Department of Medicine, C[illegible] Research Unit, DeGoesbriand Memorial Hospital and University of Vermont College of Medicine, Burlington, Vt.
This study was supported in part by grants from the National Heart [illegible], United States Public Health Service (HE-0[illegible] 169 and 09184) and from the Vermont Heart Association.
Received for publication on May 9, 1966.
*Address: University of Vermont College of Medicine, Burlington, Vt. 05401.

at least in the human being emotional and sensory stress mechanisms as such are only infrequently sufficiently cardiotoxic to produce serious lesions in an otherwise normal heart muscle whose vulnerability is not simultaneously augmented by other co-existing derangements pertaining to the wide spectrum of jointly contributing pathogenic factors

In order to understand the origin of hypoxic heart disease it is necessary to keep in mind the fundamental fact that contrary to traditional beliefs injurious myocardial hypoxia does not always result merely from a sclerotic narrowing of the coronary arterial branches[14 L] (except for extreme stenosis or occlusion) The occurrence of hypoxia in certain areas of the myocardial tissue depends rather on the *coincidence* of a locally reduced vascular oxygen *supply* (e g due to coronary atherosclerosis) and an absolute or relative exaggeration of myocardial oxygen *consumption* in other words on a local discrepancy between oxygen availability and demand The latter is specifically augmented by the catecholamine liberating and thus oxygen wasting activity of the cardiac sympathetic nerves

An acute or sustained sympathetic adrenergic overactivity is elicited by emotional and sensory stresses which are associated with central nervous stimulation of the sympathetic and the sympathetic controlled adrenomedullary system[22] Aside from their catecholamine mediated interference in myocardial oxygen economy central nervous stimuli are also responsible for stress-induced discharges of adrenal corticoids which together with catecholamine action affect myocardial electrolyte balance and for the mobilization of free fatty acids from adipose tissue as well as of other lipids possibly from the liver

Thus we will have to proceed step by step tracing the various neurogenic hormonal and cardiometabolic mechanisms which according to present-day knowledge contribute jointly to the mass mortality from degenerative heart disease in highly civilized prosperous nations notably in the U S A

Particular attention will hereby be paid to the behavior of catecholamines and adrenal corticoids in view of the well known potential cardiotoxicity of the former[22] and its marked exaggeration by the latter[14 1]

## II Emotional and sensory stress induced liberation of catecholamines

Karplus and Kreidl's[16] discovery of functional connections between the central nervous and the peripheral sympathetic systems and Cannon's[17] classic studies concerning the activation of the latter under the influence of emotional and sensory stimuli laid the foundations for today's concepts of psychosomatic interrelationships in cardiovascular physiology and pathophysiology

Both the cerebral cortex the hypothalamus and the reticular substance[18 19] participate in the activation of catecholamine liberating sympathetic pathways within the framework of mental processes Whether reciprocal feedback mechanisms (e g retrograde stimulation of central structures by peripherally discharged epinephrine[9-1]) are hereby involved remains a matter of conjecture

Significant and sometimes very marked augmentations of urinary catecholamine excretion have been observed with great regularity under various kinds of emotional and sensory stresses and tensions such as scholastic examinations[22 23] admission to a hospital[4] airplane flying[22] viewing exciting films[4] performing exacting industrial or office work with annoying noise and light disturbances[24] etc Even the anticipation of an uncomfortable experience[3] can be associated with an elevation of the urinary catecholamine level

In general it can be said that all anxiety provoking situations are characterized by a high excretion of epinephrine with only slight or no increase in norepinephrine[22] whereas under attitudes of aggressiveness the excretion of norepinephrine comes more to the foreground[19 22] Augmentations of urinary catecholamines were also observed under conditions of pleasurable excitement[4] and sexual arousal[4] By contrast the viewing of peaceful serene nature films was accompanied by a drop in the catecholamine excretion below the control level

Diurnal fluctuations chiefly of ep

rine are of considerable magnitude with peaks in the afternoon and low points after midnight.

The catecholamine metabolite vanillin mandelic acid (VMA) was likewise found to be augmented in the urine in states of anxiety, tension and anticipation, e.g., while driving a car, etc.

During states of mania in psychotic patients the excretion of epinephrine was found to be increased with little or no change in norepinephrine. Mental depressions do not seem to exert a characteristic influence on the production of catecholamines.

Temperamental differences between high strung ambitious personality types and their placid easy going counterparts appear to be reflected in a higher urinary norepinephrine excretion in the former. Low levels of catecholamine excretion were observed in emotionally stable primitive African nomadic natives.

In monkeys plasma levels of norepinephrine rose during various experimentally induced emotional disturbances. Increases in epinephrine were most closely connected with situations of uncertainty and threat. Similar reactions of the plasma catecholamines occur in man under intensive emotional stress. During 6 minutes of a milder mental stress (arithmetic) no significant changes in the plasma norepinephrine concentration were observed.

In summary, an augmented liberation of adrenosympathetic catecholamines appears to be well established as a typical sequel of emotional and sensory central nervous stimulation. Epinephrine discharges seem to be prevalent mainly in situations of passive anxiety, whereas norepinephrine is mobilized during attitudes of aggressiveness and violent action.

### III Influence of central nervous, emotional, and sensory stimuli upon cardiac rhythm, dynamics, and ECG

Cardiac acceleration occurs under a great variety of emotionally significant circumstances as a catecholamine mediated result of centrally elicited sympathetic nerve stimulation.

Sudden fright may be associated with a short lasting vagotonic bradycardia or even cardiac standstill. Anxiety and

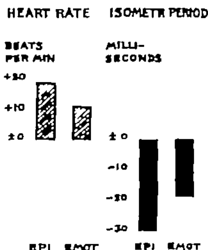



Fig. 1. Adrenergic effects of infused epinephrine (0.1 μg/kg/min.) and of emotion induced catecholamine action (students immediately before examination) on heart rate and isometric tension period of left ventricle. Shortening of the latter is a sensitive criterion of adrenergic increase in myocardial oxygen consumption. (For detail see Raab et al. Cardiologia 33:350, 1958.)

anticipatory tension, on the other hand, evoke moderate to marked accelerations of the heartbeat. This is the case, for example, before imminent scholastic examinations and contests (Fig. 1), during exciting discussions, in response to verbal stimuli, during arousal of feelings of hostility, watching sports games, etc. Likewise intellectual effort under pressure, as in performing supervised mental arithmetic, and sensory annoyances such as noise or flickering light induce various degrees of tachycardia.

The cardiac output is augmented under the aforementioned emotional and sensory stimulations. The usual exercise induced cardiac acceleration was found to be further exaggerated during emotional stress or acoustical annoyances, and the postexercise deceleration was retarded.

An increase in the heart rate can be elicited by symbolic stimuli, e.g., by the mere discussion of exercising, and conditioned reflex mechanisms are apt to maintain acquired cardiac chronotropic reactions to conditioning stimuli over long periods of time.

Shortening of the isometric tension period of the left ventricle is a sensitive criterion of adrenergic inotropic action

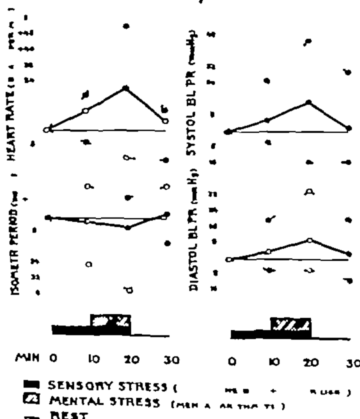



Fig. 2. Ranges (dotted lines) and averages (solid lines) of deviations from resting heart rate, isometric tension period, systolic and diastolic blood pressure in response to standard sensory plus mental stresses (20 minutes of rhythmic telephone bell ringing and flickering light, 10 minutes of mental arithmetic) followed by a 10 minute recovery period. (From Raab and Krzywanek, American Journal of Cardiology 16:42, 1965, by permission.)

Accordingly, it occurs during both sensory[24] (noise, flickering light) and mental stresses[11,28] (Figs. 1 and 2).

Emotion-induced cardiac acceleration and corresponding changes in the electroencephalogram make their appearance simultaneously.[38]

In two small groups, one of high-strung and the other of placid individuals, no significant difference was found in total 48 hour average heart rates.[4] On the other hand, in a larger series the resting heart rate of emotionally irritable, tense persons proved to be significantly higher than that of leisurely individuals who had a more neutral temperament.[24] Cardiac responses (acceleration and shortening of the isometric tension period) occurred likewise on a higher level in the former group[28] (Fig. 3), and the relative length of the left ventricular systole in per cent of the cardiac cycle was prolonged in the emotionally irritable subjects.[28]

Besides tachycardia[44,49] and a combination of tachycardia with feelings of anxiety,[7] experimental cortical and sub-

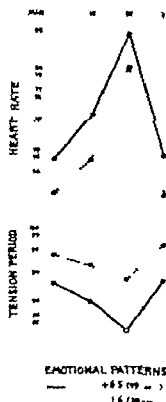



Fig 3 Cardiac responses to the same test procedure as in Fig 2 grouped according to personality patterns 49 subjects with high 28 with low emotional excitability (according to self evaluation by questionnaire and point scoring) The cardiac sympathetic resting tone and stress response is higher in the excitable subjects and lower in the placid ones (From Raab and Krzywanek American Journal of Cardiology 16 42 1965 by permission)

cortical stimulations can also elicit other abnormalities of the cardiac rhythm including vagal bradycardia depending on the location of the stimulated areas

Ectopic beats and other arrhythmias were thus artificially provoked and inversions of T as well as S T segment displacements appeared to be indicative of myocardial hypoxia It is worthy of note that under such experimental conditions the epinephrine content of the heart muscle was markedly augmented presumably because of neurogenic discharges from the adrenal medulla whose epinephrine stores were simultaneously found to be reduced

Local stimulation of the stellate ganglia on the other hand was followed by an accumulation of norepinephrine in the myocardium Both catecholamines if present in excess are known to produce hypoxic changes in the electrocardiogram

Alterations of the cardiac rhythm and the electrocardiogram similar to those experimentally induced by stimulation of the central nervous system are not infrequently observed as spontaneous events under emotional stresses They include supraventricular and ventricular premature contractions paroxysmal atrial nodal and ventricular tachycardia and presumably due to vagal participation paroxysmal atrial fibrillation and A V block especially in the presence of arteriosclerotic vascular changes in the vicinity of the sinoatrial node and the A V conduction system

Inadequate compensatory dilatability of the coronary arteries which supply the myocardium of the left ventricle facilitates the appearance of anoxic patterns in the electrocardiographic ventricular complex under emotionally provoked neurogenic catecholamine action This occurs in a similar fashion when manifestations of ventricular anoxia are evoked by mere sympathetic stimulation when coronary dilatability is artificially impaired

Such electrocardiographic changes especially inversion of T and displacement of S T have been observed under a variety of acute or prolonged emotional stimuli and stresses such as verbal stimulation watching sports games violent arguments admission to prison listening to stirring music impending surgery and other states of anxiety and emotional excitement (Fig 4) including anxiety neuroses and hypnotically suggested emotionally stressful situations

Inversions of T and elevations of the S T segment were also recorded in neurotic baboons with intact coronary arteries

Anxiety seems to be a particularly effective emotional element in eliciting myocardial ischemic changes but no clearly specific differentiations have been made between patterns provoked by anxiety and those provoked by other emotional stresses They all point to catecholamine mediated neurogenic interferences in myocardial oxygen economy

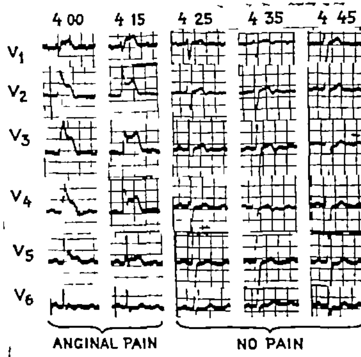



Fig 4 Anginic upward displacement of S T segment during emotion induced attack of angina pectoris subsiding within 25 minutes

**IV Emotion induced catecholamine mediated angina pectoris and sudden death**

The nearly 30 year old long rejected or disregarded concept of a fundamental causal involvement of myocardial oxygen consumption–augmenting catecholamines in the clinical syndrome of angina pectoris is today so widely accepted and adopted[65, 183] that it does not require a detailed repetition here

The only important amplification of its basic principle was contributed by von Euler s discovery in 1946 of norepinephrine as the intramyocardially liberated neurohormone of the sympathetic nervous system[184]

The typical provocation of anginal symptoms by acute emotional arousal[185] rather than by chronic emotional tensions[186] is one of the best known examples of psychosomatic pathology Its causal connection with catecholamine liberating emotional central nervous stimulations (see Section II) elevated catecholamine level in the blood plasma[55] increased catecholamine metabolites in the urine[186] and the familiar catecholamine induced increase in myocardial oxygen consumption[187] appears to be well established

Such emotional stimuli and catecholamine discharges from the adrenal medulla and from the cardiac sympathetic nerve terminals in order to elicit myocardial hypoxia in circumscribed areas of the myocardium[188] require in general the predisposing presence of atherosclerotic coronary narrowings This constellation could be experimentally duplicated by combining cardiac sympathetic stimulation or injection of catecholamines with an artificial limitation of coronary dilatability[67] (Fig 5)

Significantly various antiadrenergic measures such as the administration of tranquilizing drugs[89, 11] thoracic sympathectomy[112] epinephrine secretion reducing x ray irradiation of the adrenal glands[13] emotion suppressing antithyroid treatment[11] and ganglionic and beta receptor blockers have been found to be useful in the treatment of angina pectoris

The usually short duration of anginal attacks even if the underlying emotional

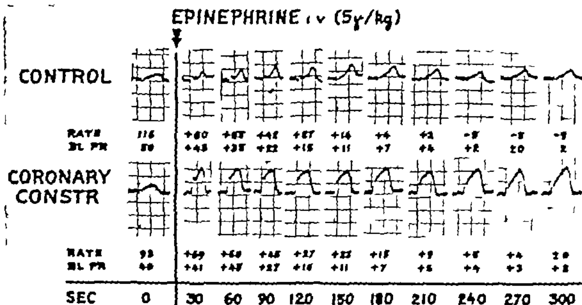



Fig. 5. Hypoxiating (S-T depressing) effect of infused epinephrine greatly intensified by limitation of compensatory coronary dilatability through snugly fitting but not occluding ligature. (From Raab et al. American Journal of Cardiology 9:4-5, 1962, by permission.)

situation persists suggests some self-regulatory mechanism such as possibly a vasodilating effect of accumulated lactic acid.[13]

Sudden unexpected death has been observed with relative frequency in close time relationship and evident causal connection with acute emotional events, e.g., an excited argument, a stressful interview, the receipt of some crushing news, or a sudden fright.[116,13]

For obvious reasons the exact physiological and biochemical mechanisms involved at the critical moment remain unknown as a rule, but it can be assumed by inference that either ventricular fibrillation or cholinergic ventricular standstill have occurred,[1] the latter being more likely the result of fright than of anger or grief.

In more than 90 per cent of a series of instances of unexpected death occurring within 1 hour or less after the onset of symptoms at least some degree of coronary atherosclerosis could be detected[173] as a presumably predisposing factor. However, exceptions to this rule exist. In two cases concerning young, generally healthy persons who died suddenly without any explanatory antecedents or significant autopsy findings the major coronary arteries were free of atherosclerosis, but both subjects presented extraordinarily high concentrations of catecholamines in the left ventricular myocardium.[1,3,1,4] Possible emotional factors consisted of an argument about 6 hours before death in the one case (reported after publication) and admission to a hospital, also several hours before death, in the other.

Disseminated necrotic and fibrotic foci resembling those which are experimentally produced by the injection of catecholamines[13] have frequently been found in the subendocardium after sudden unexplained death.[1,1] They suggest the preceding occurrence of repeated cardiotoxic adrenergic episodes since even in complete anoxia the development of necroses requires at least 18 minutes.[1]

Interestingly, in cases of sudden unexplained death disseminated areas of potassium depletion were detected in the ventricular wall before the appearance of histologic alterations,[194] apparently in analogy to similar intramyocardial spotty displacements of potassium seen after the injection of epinephrine.[17]

Emotion induced centrally triggered acute catecholamine discharges can be assumed to play a dominant role both in the production of anginal attacks and in the causation of some types of sudden unexpected death. The observation of cardiac standstill resulting from a coincidence of vagal stimulation with discharges of vasopressin[1] may be of significance for the explanation of sudden deaths from fright.

### V Centrally and emotionally induced myocardial necroses and infarctions

Multiple necrotic foci and nonpenetrating infarctions in the myocardium of animals have frequently been observed subsequent to caustic[14], mechanical[76] and electrical[73] stimulations of the central nervous system (cortex, hypothalamus, brain ventricles). The latter were accompanied by arrhythmias of apparently mixed sympathetic and vagal origin.[8] Simultaneous electrocardiographic manifestations of myocardial ischemia were similar to those elicited in man by head injuries or by spontaneous cerebral accidents[136,137] (which are followed by an augmented excretion of catecholamines[138]) or evoked by the experimental injection of catecholamines.[11,134]

Intensive mechanical[138] or chemical[12] or prolonged electrical[134] stimulations of the stellate ganglia, which cause an accumulation of norepinephrine in the myocardium,[75] produce identical alterations of the electrocardiogram and disseminated focal necroses in the heart muscle.

The same pattern of myocardial metabolic derangements and destruction was found to occur in animals under experimental conditions in which emotional and/or sensory disturbances constituted a prominent feature, such as repeated faradic shocks,[117,[illegible]] light flashes and noise, physical restraint[11,138,139,14] in rats and caging[140,141] or neurosis producing annoyances[83,84] in wild baboons (Fig. 6). Frustrating interferences in the access to food in

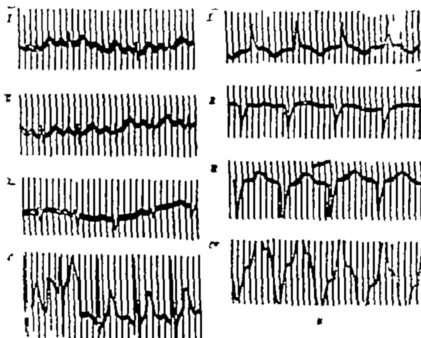


Fig. 4 Left ventricular infarction pattern in a baboon with neurosis induced by frequent changing of light (dark rhythm) and of feeding intervals during several months. At autopsy myocardial necrose, patent coronary arteries. (From Cherk... rch ... tol ... Eksperimentalnaya terapiya 6 2 1959 Medgiz Moscow.)



Fig 7 Myocardial necroses produced in wild rats by anxiety (in 69 per cent of series) One week exposure to noise of tape recorded cat rat fight (From Raab et al Proceedings of the Society for Experimental Biology and Medicine 116 665 1964 )

white rats and the provocation of anxiety in gray wild rats by means of a tape recorded noisy cat rat fight[14] (Fig 7) elicited identical destructive lesions in the left ventricular myocardium

Centrally depressing ganglionic blocking antiadrenergic and catecholamine depleting drugs or their combination prevented the occurrence of sympathogenic myocardial necroses with different degrees of effectiveness[10,10]

It should be pointed out here that in practically all of the above listed instances of experimental centrally and peripherally elicited and emotion induced sympathogenic myocardial necroses or microinfarctions the coronary arteries were free of discernible lesions

This seems to indicate that the necrotizing catecholamine discharges must have been quite massive Analogous conditions occur in cases of pheochromocytoma which frequently causes disseminated myocardial necroses in the absence of coronary atherosclerosis[14] A prolonged duration of adrenergic overactivity constitutes a

pathogenesis aggravating element.[144, 146] Finally, the presumable participation of adrenal corticoids as a catecholamine cardiotoxicity potentiating factor needs to be taken into consideration. This will be done in Section VI.

The regularly subendocardial location of the catecholamine induced and sympathogenic foci of necrosis is probably to be explained by microcirculatory mechanisms as discussed elsewhere.[19, 22]

The origin of myocardial lesions which have been reported as resulting from vagal stimulation[145] still remains to be elucidated.

As far as the applicability of the here described principles of centrogenic and emotion induced myocardial destruction to human pathology is concerned, we have to rely—aside from the abundant indirect experimental evidence—on clinical criteria. These consist essentially in the time connection between the occurrence of emotional stimuli and significant electrocardiographic, cardiodynamic and blood chemical changes and retrospective as well as prospective epidemiologic data.

The prevailingly adrenergic responses of the human heart to emotional stimuli, their documented connection with catecholamine discharges and the role of the latter in anginal attacks[147] and sudden death[133, 134] have been discussed in the preceding sections. We have *now to examine* the part played by emotional and sensory stresses and irritations in the origin of structural injury to the human heart.

In *doing so*, we will exclude from the beginning the instances of thrombotic coronary obstruction. The *clinical* diagnostic term "coronary thrombosis" has been grossly misused in the past. Today it is known that in a high percentage (up to more than 50 per cent) of clinically diagnosed infarctions no obstructing thrombi can be ascertained.[148, 149] Moreover, some investigators suspect that even detectable thrombi may constitute a secondary sequel rather than the direct cause of infarction and myocardial tissue necrosis.[150]

The possibility of a direct relationship between emotional factors and thrombus formation, e.g., by way of an acceleration of blood clotting in high-strung individual,[3] is still problematic.[151]

The originally tempting but long-discredited idea of coronary spasms as a cause of myocardial hypoxia was recently revived on the basis of apparent coronary angiographic evidence.[152, 153] However, since augmented myocardial oxygen consumption is physiologically associated with coronary dilatation rather than with constriction[19] and since cardioangiographic contrast media can temporarily reduce the coronary flow,[154] the possibility of artifacts caused by the introduction of such materials into the coronary arteries is not yet ruled out with certainty.

H. B. Sprague[157] has challenged the concept of a significant causal involvement of emotional stresses and tensions in the high incidence of ischemic heart disease in our civilization because stresses of various kinds have always been an inherent element of human life. This objection would have greater weight if the cardiac pathogenicity of emotional stresses were simply regarded as an isolated noxious factor by itself and not as just one additional contributory—although often decisively contributory—element within the plurifactorial framework of hypoxic myocardial (not merely coronary vascular) disease. A possible participation of emotional neurogenic elements in atherogenesis will be discussed in Section VII.

At this juncture we are dealing with the profound interference of emotionally induced disturbing neurohormonal mechanisms in a myocardium whose metabolic integrity is more often than not already threatened by other civilization dependent detriments such as diet aggravated atherosclerosis and oxygen wasting adrenergic overactivity due to a lack of exercise[1, 8] and/or to tobacco smoking. In other words emotional stress appears in many instances to provide only "the last straw on the camel's back," but as such it is to be taken seriously.

Close time connections between emotional upheavals and the occurrence of cardiac accidents are too common to require specific references beyond those listed in Section IV. The so-called "anniversary infarctions" precipitated by accentuated emotions on personally meaningful anniversary days[155] may be mentioned as an example.

However, beyond such acute connec-

dences the prolonged persistence or frequent repetition of potentially noxious emotional stimuli can be reasonably assumed to act in man as under similar model conditions in the above described striking animal experiments. The apparently high incidence of infarctions in night shift workers[7,74] may be compared to the myocardial lesions produced in baboons by alterations of the daily light and darkness rhythm.[84]

Several epidemiologic studies have provided suggestive evidence for an at least partial involvement of emotional stress factors *in the pathogenesis of myocardial infarctions*.[114] Extensive statistics among American physicians[164] and other professional groups[165] revealed a distinct concordance between the degree of occupational emotional stress (e.g., among physicians the range was between the extremes of harassed general practitioners on the one hand and peaceable dermatologists on the other) and the incidence of infarctions with the exaggerated ingestion of atherogenic animal fats being recognized as an additional contributing element.[164]

Russian investigators[162,164,166] arrived at similar conclusions comparing the cardiac ischemic morbidity among intellectuals and manual laborers not however without also calling attention to the pathogenically significant[165,167] difference in physical activity between these occupational groups. The same ambiguity applies to statistics from Germany[168] and India.[169] In this respect of interest is the fact that among the urban white collar workers in Moscow one particularly emotionally tense group namely the highly competitive scientists proved to be more susceptible to infarctions than did nonacademic employees.[164]

On the other hand in a study of salaried employees within a large American industrial population[170] the incidence of infarctions was found to be relatively low among executives presumably as a result of greater personal satisfaction and stabilization provided by having reached a high ranking secure job level.

In the so-called Western Collaborative Group Study[171] concerning evaluation of three cardiac risk factors namely abnormal lipoprotein patterns hypertension and the high strung ambitious personality type A (which is associated with a high excretion of catecholamines[17] and their derivative VMA[172]) the latter factor proved to be the most important single prognostic criterion.

A comparative freedom from degenerative heart disease observed among nomadic Somali herdsmen whose catecholamine excretion is low[44] and among Italian immigrants in Roseto Pennsylvania[173] (despite the massive consumption of fat by both groups) has been interpreted as suggesting a favorable influence of simple tranquil and carefree living conditions.

*It must be admitted that* despite their suggestive appearance the above listed epidemiologic investigations are fraught with inevitable uncertainties inherent in the difficulties of differentiation between external emotional load and individual reaction as well as due to the interference of ethnic social and unidentified somatic factors. Neither the Western nor the Roseto study results have remained unchallenged.[174,175]

A high cardiac sympathetic tone as expressed by a consistent elevation of the heart rate and stress response seems to constitute a partially common denominator of emotional imbalance[4,176] on the one hand and of proneness to ischemic heart disease on the other.[176,177] However this presumably important factor has not yet been studied with sufficiently systematic thoroughness.

An interesting hypothesis being advanced by Mine[78] is that besides the well established cardiac detriments of emotions without motion[179] the opposite namely rationally motivated but not emotionally supported physical action as a feature of Western civilization may likewise interfere in myocardial metabolic health by some as yet undefined nervous mechanisms.

**VI Emotions, adrenal corticoids, and myocardial damage**

One particularly important emotion induced neuroendocrine phenomenon is still underexplored with regard to its probable significance in myocardial pathology namely the augmented secretion of adrenal corticoids as an essential corollary of the well known potentially cardiotoxic

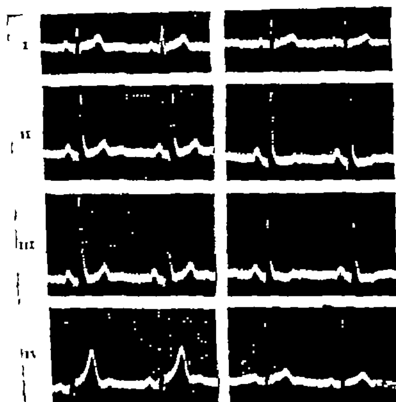



Fig. 8. Inversion of T wave, healthy young volunteer persisting 4 weeks after injection of epinephrine following pretreatment with desoxycorticosterone acetate. (From Raab: American Heart Journal 24: 365, 1942.)

overproduction of adrenergic catecholamines.[18,41] It may be considered to be the possible cause of an even more cardiotoxic corticoid-catecholamine interaction.

Selye's[1] discovery of a marked "sensitization" of the heart muscle by corticoids to the necrotizing cardiotoxicity of both injected catecholamines and stress-induced catecholamine action[17] has been fully confirmed[7,89,199,111] (Fig. 8). This applies also to a corticoid-induced intensification of the destructive effect of experimental local myocardial hypoxia.[19] A combination of catecholamine-induced metabolic hypoxia with an ACTH-mediated corticoid-induced superimposed loss of potassium[18,19] from the heart muscle[17,171,181,184] seems to constitute the underlying mechanism of myocardial destruction under stress (Fig. 9).

Physiologic studies have revealed the fact that the pituitary-mediated secretion of adrenal corticoids, especially of the 17-hydroxycorticoid (17-OHCS), is augmented by electrical stimulation of certain diencephalic as well as cerebral cortical areas[187,11] simultaneously with the neurogenic libertation of adrenomedullary and sympathetic catecholamines, and by similarly acting emotional central stimuli.

Increased urinary excretion or prolonged elevation of the plasma level of 17-OHCS and other corticoids were observed in animals under conditions of anxiety or aggression[41] and also in both animals[189] and man[7] in response to sensory stimuli. In human beings the same occurs under various comparable emotional stresses such as situations constituting a threat to security, survival, self-respect, or crucial personal interrelationships,[... ] e.g., impending surgery, parachute jumping, long-distance flying, scholastic examinations, embarrassing interviews, sports competitions, etc.

In older persons the urinary 17-OHCS excretion seems to be generally higher.[193]

Although it was found to be low ...

HYPO THALAMUS
PITUITARY
SYMPATH N
ACTH
NOREPINEPHR
SPLANCH N
K+
EPINEPHR
K+
17-OHCS

Fig 9 Socioeconomic emotional and sensory stresses stimulate in the cerebral cortex and hypothalamus (a) the sympathetic nervous system which releases potentially myocardium hypoxiating epinephrine from the adrenal medulla and norepinephrine from the postganglionic nerve endings within the heart muscle and (b) the anterior pituitary which by means of ACTH secretion release 17 hydroxy corticosteroid from the adrenal cortex thus causing losses of potassium through the kidney and losses of potassium from the heart muscle Especially in the presence of coronary atherosclerosis is the catecholamine induced wastage of myocardial oxygen combined with 17 OHCS induced loss of potassium apt to become critically cardiotoxic

cyclic states of mania [94] the 17 OHCS excretion is rather regularly elevated during emotional depression [80 73 135 246]

The suggestion of anxiety producing situations under hypnosis evokes rises in the plasma 17 OHCS (hydrocortisone) levels similar to those in the waking state [246 98] On the other hand the hypnotic trance as such tends to reduce the plasma concentration of the 17 OHCS [83]

The viewing of pleasant and relaxing nature films was likewise accompanied by a lowering of the level of plasma 17 OHCS [246]

No significant difference in the excretion of 17 OHCS and 17 ketosteroid was observed between the high strung A and the placid B personality types [33]

The excretion of aldosterone was found to be elevated in professional persons during the presentation of scientific papers and during examinations [39]

Both catecholamines and corticoids are liberated by the same directly applied central nervous as well as emotional and sensory stimuli (see above) and both have been shown to rise simultaneously under emotional stress [75 61]

This parallelism may be of fundamental importance for the origin of the demonstrable cardiotoxic effects resulting from artificial central emotional or sensory stimuli Such a dual action can be concluded from the marked intensification of myocardial destruction by stresses catecholamine administration and experimental myocardial hypoxia when combined with exogenous corticoid administration [11 1 1 7 118 114 131 499] It is also suggested by the fact that catecholamine cardiotoxicity is greatly increased (up to sixteen fold) in the presence of adrenal cortical hypertrophy as it develops for example in long isolated animals [197 63]

*Potentiation of the liberation of free fatty acids by epinephrine under the influence of cortisone appears to be a related phenomenon* [299]

A feedback mechanism between the central nervous origin and the peripheral somatic repercussions of anxiety is made probable by the anxiety induced liberation of both catecholamines and corticoids on the one hand (see above) and by the anxiety feelings evoked by an excess of both of these hormones on the other hand [1 194]

From the point of view of cardiac pathogenicity it is of interest that both emotional stresses and physical exercise cause sympathetic stimulation and catecholamine discharges but that only the former are associated with a simultaneous liberation of catecholamine toxifying adrenal corticoids whereas exercise does not elicit this potentially detrimental combination [193 127 133 117 75 88 127] This may in part explain the remarkable destructiveness of emotional and sensory stimuli observed in animals even with normal coronary arteries [11 14 131 10] as compared with the near absence of such destructiveness after

And from the high incid... of my... [illegible]
... [illegible]

muscular exertion How far this principle applies also to human beings is not yet adequately clarified

It is known that during the night and during sleep the production of catecholamines recedes to some extent [illegible] whereas the plasma corticoids rise between midnight and the early morning hours [illegible] especially under prevailing stressful conditions [illegible] This latter phenomenon may have some bearing on the problem of unexpected nocturnal deaths [illegible]

### VII Emotions sensory stress and the vascular system

Much of the existing skepticism with regard to the pathogenic role of emotional and sensory stresses in ischemic heart disease [illegible] is due to a widespread misunderstanding by which these stresses are alleged to be the primary or even the sole cause of severe myocardial lesions in man It is all too often being overlooked that ischemic heart disease usually arises from a coincidence of several variable vascular and nonvascular jointly contributing derangements among which stress is only one constituent albeit often a crucially important one

The profound influence of central nervous emotional and sensory stress stimuli on the primarily nonvascular features of myocardial metabolism has been discussed in the preceding sections Whether and to what extent such neurogenic and hormonal factors contribute also to vascular structural alterations notably to coronary atherogenesis has not yet been extensively investigated

The possibility of markedly aggravating aortic and coronary atherogenesis through experimental interference in the central nervous system by prolonged and repeated electrical and pharmacodynamic stimulations of the hypothalamus could be demonstrated in cholesterol fed rabbits [illegible]

Direct angiotoxic effects of injected or secreted catecholamines or of peripheral sympathetic nerve stimulation not only concern the arterial media (so called Monckeberg sclerosis) but can also produce thickening and inflammatory changes of the intima [illegible] Similar apparently stress induced vascular changes have been observed in animals [illegible]

In addition to direct chemical injuries inflicted on the arterial walls by their exaggerated action the catecholamines seem to contribute also to the infiltration of lipids into the intima by elevating the blood lipid level Mobilization of free fatty acids (FFA) from adipose tissue occurs promptly under central nervous [illegible] sympathetic and catecholamine influence [illegible] and consequently under emotional stress (chiefly fear and anger) [illegible] including intensive mental effort [illegible]

The serum cholesterol level rises under provocation by central nervous stimuli [illegible] and under emotionally stressful conditions both in animals and human beings [illegible] even during mere anticipation of an impending stress [illegible] Differences between the basic serum cholesterol level of high strung and irritable persons on the one hand and that of placid easy going ones on the other [illegible] were however not observed with regularity [illegible]

Serum triglycerides were found to be augmented in some excitable individuals [illegible] under stress [illegible]

On the basis of the hypothesis that catecholamine mobilized free fatty acids are transformed in the liver into triglycerides and phospholipids [illegible] one may suspect a sympathetic triggered mechanism participating in the origin of potentially atherogenic hypercholesterolemia This would represent the opposite of the beneficial reduction of both the sympathetic tone and the serum cholesterol level by physical training [illegible] It would further resemble the blood glucose elevations under stress and sympathetic activity on the one hand [illegible] and the frequently increased blood glucose level of coronary prone individuals [illegible] on the other

These apparent blood chemical interrelationships suggest one more possible dimension of potentially cardio detrimental sympathetic overactivity involving not only the myocardium itself but also the latter's supplying coronary arteries via interference in lipid metabolism

Finally arterial hypertension has to be considered to be a partially neurogenic partially hormonal and often emotionally aggravated cardiac risk factor

Elevations of the diastolic pressure impose an increased mechanical load on the heart muscle and contribute to a hypo

ating hemodynamic compression of the left ventricular subendocardial arterioles.[10,12] This becomes all the more critical if myocardial oxygen consumption is augmented by simultaneous sympathogenic local catecholamine action.

Causal connections between central nervous stimulation, emotional excitement, attitudes of hostility, frustration, and tensions on the one hand, and acute or sustained elevations of the blood pressure on the other, have long been recognized.[8,241,242] They are particularly emphasized by the Russian school of thought.[244]

Sensory stresses such as noise and light stimuli can likewise produce transient or prolonged hypertensive reactions in animals[44,142] and man[47,48] (Figs. 2 and 3).

In pluricausal, so-called "essential" hypertension at rest, the level of catecholamines in the plasma does not usually exceed normal limits.[247,248] Mineralocorticoid action, probably by affecting vascular electrolyte metabolism,[247,49] increases the arterial contractile response to catecholamines.[47] Whether the irregularly observed augmentation of aldosterone production in "essential" hypertension[8] can be attributed to emotional factors remains in doubt.

Finally, high levels of blood pressure seem to contribute to atherogenesis[1] and thus may constitute an additional possible pathogenic link between emotional stresses and myocardial damage.

### VIII. Emotional stress and congestive heart failure

Emotional stresses have to be considered as factors contributing both to cathecholamine- and/or corticoid-induced direct myocardial damage and to elevations of the blood pressure, all of which may lead separately or jointly to congestive heart failure, especially in the presence of coronary atherosclerosis or valvular lesions.

The capacity of augmented catecholamine action to elicit left ventricular failure and pulmonary edema[2,14] has been demonstrated many times by the injection or infusion of epinephrine, norepinephrine[11,12] or isoproterenol[14] and by the common occurrence of death from congestive heart failure in patients with pheochromocytoma.[141,250]

Equally common is the development of congestive heart failure in cases of adrenocortical tumors.[250] Augmented fatal catecholamine cardiotoxicity has been observed under spontaneous corticoid overaction as it occurs in rats under the influence of prolonged isolation.[87,88] Thus an excess of catecholamines as well as of corticoids, a joint overproduction of both of which is a characteristic manifestation of emotional stress, ranks manifestly among the causative or aggravating mechanisms in congestive heart failure, presumably due to combined hypoxiating catecholamine and potassium-depleting corticoid action (see Section V, f).

Signs of congestive failure developing under emotional stress have been observed also in anthropoid apes.[91,149]

Certain metabolic alterations found in the failing myocardium closely resemble those which are typically produced by exaggerated catecholamine interference.[117,1] However, in the already damaged failing human heart muscle, the norepinephrine content is reduced,[25,254] whereas epinephrine tends to be increased.[3] The reason for these changes is not yet clear, but they can scarcely invalidate the concept that initially an emotion-induced overproduction of catecholamines may have played an important role in many instances in injuring the myocardium before the latter went into failure and secondarily lost part of its norepinephrine stores.

In the majority of a recorded series of clinical cases of congestive heart failure, chronic emotional difficulties as well as acute conflicts appeared to represent a significantly precipitating element.[257] This was substantiated by the observation that in such patients deliberately induced acute emotional and mental stresses provoke a rise in central venous pressure.[258]

The sensory stresses of heat and humidity are likewise apt to elicit adrenergic hemodynamic and cardiac manifestations and to markedly aggravate an existing state of congestive heart failure.[39]

Some of the alterations in electrolytes, phosphates, proteins, enzymes, etc., which are detectable in the failing heart muscle[14,16] probably represent secondary

sequelae of pre-established myocardial lesions rather than specific primary derangements of neurohormonal and hormonal origin.

The overproduction of aldosterone, another characteristic feature of the congestive failure syndrome, may likewise be interpreted as a secondary complicating phenomenon.[11,4]

## IX. Emotion- and sensory-oriented therapy and prevention

Therapy will be discussed here only in so far as it is aimed at the reduction of emotion- and sensory-induced central nervous overstimulation and at the resulting overproduction and overactivity of cardiotoxic catecholamines and corticoids.

Beyond protection of the patient from emotionally strenuous situations, annoying noises, glaring or unsteady light and uncomfortable atmospheric temperature and humidity, the application of specific drug treatment is indicated according to circumstances.

Animal experiments have shown that the development of stress-induced[[illegible]] or peripheral sympathetic stimulation induced[[illegible]] myocardial necroses can be prevented by treatment with centrally tranquilizing,[[illegible]] peripherally ganglionic blocking,[[illegible]] catecholamine depleting[[illegible]] and adrenolytic[[illegible]] drugs. It appears that tranquilizing drugs are more effective in controlling sympathetic neurosecretory than adrenal cortical overaction.[[illegible]]

Emotionally induced and mental stress induced cardiac accelerations can be counteracted by beta-adrenergic blockers[[illegible]] and monoamine oxidase inhibitors[[illegible]] which are believed to inhibit ganglionic and postganglionic transmission.[[illegible]]

Angina pectoris, the classic example of emotion- and catecholamine-provoked acute myocardial hypoxia in the presence of coronary atherosclerosis,[[illegible]] can be ameliorated or caused to disappear by a variety of antiadrenergic measures: vagotropic and sympathoinhibitory,[[illegible]] carotid sinus pressure during the attack,[[illegible]] catecholamine reactivity reducing and sedating antithyroid treatment,[[illegible]] adrenomedullary activity suppressing roentgen irradiation of the adrenal glands,[[illegible]] cardiac sympathectomy,[[illegible]] tranquilizers such as meprobamate[[illegible]] and others,[[illegible]] monoamine oxidase inhibitors,[[illegible]] beta-receptor blockers[[illegible]] and a new, apparently plurifunctional drug, Segontin.[[illegible]]

Probably the most powerful antiadrenergic and myocardial oxygen economy restoring, preventive and rehabilitative measure is cautiously progressive but ultimately vigorous regular physical activity. It gradually lowers the exaggerated cardiac chronotropic and inotropic sympathetic tone of sedentary and tense individuals and raises the oxygen-preserving vagal tone.[[illegible]] In ischemic areas of the heart muscle it promotes the development of collaterals.[[illegible]] Moreover, animal experiments by Selye[[illegible]] and Bajusz[[illegible]] suggest that repeated exercising contributes to the accumulation of an augmented protective reserve of potassium in the myocardial tissue, whereby neuroendocrine mechanisms are presumably involved.[[illegible]]

The emotionally equilibrating effects of regular exercising are well known,[[illegible]] and so are the psychological benefits of post-infarction physical rehabilitation.[[illegible]]

Combinations of periods of environmental emotional relaxation with physical training and with the inculcation of permanent sensible health habits have been systematically organized in Europe over the last four and a half decades on a very large scale in about three thousand rural reconditioning centers. These are located mostly in attractive, serene mountainous areas and accommodate annually about five million fatigued and tense pre-patients and patients for physical and emotional reconditioning. Some of these centers offer instruction in handicrafts and other hobbies for creative, emotionally satisfying utilization of leisure time.[[illegible]]

Studies from European centers have revealed a nearly uniformly improved subjective well-being of the trainees, and 4 to 6 weeks of combined environmental emotional and physical reconditioning have also been followed by a measurable diminution of the cardiac sympathetic tone. This was manifested chiefly by a slower heart rate at rest and during exercise[[illegible]] and by a prolongation of the isometric period of the left ventricle,[[illegible]] which persisted for periods of several months to over 1

year.[illegible] The blood pressure responses to standard exercise were likewise frequently reduced.[illegible] In the majority of persons with signs of ischemic heart disease, the electrocardiogram at rest and/or during exercise and the ballistocardiogram were improved or normalized, and the serum cholesterol level was lowered.[illegible]

It seems to be probable that the emotionally appealing rural and mountainous environment of these centers exerts its beneficial influence in a way related to the decrease in the production of catecholamines[illegible] and 17-hydroxycorticosteroids[illegible] which was observed during the viewing of scenic nature films.

Experience in the reconditioning centers has shown that the strong emotional impact of an extended close exposure to natural pleasant surroundings and the gain in self-confidence after an improvement in physical fitness make the trainees particularly amenable to the acceptance and maintenance of indefinitely continued health habits.

## X. Conclusions

An up-to-date insight into the complex problem of emotion- and sensory stress-induced derangements of myocardial function and structure requires coordination and integration of numerous splinter data from the international literature pertaining to the divergent disciplines of biochemistry, physiology, neuroendocrinology, pharmacology, pathology, clinical medicine, psychology, epidemiology, and sociology.

In spite of inevitable omissions and a multitude of still unresolved questions with regard to details, the foregoing attempted review of present-day knowledge warrants the definite conclusion that emotional and sensory stress factors are directly responsible as contributory, if not exclusive, causative elements in such myocardial abnormalities as tachycardia, various arrhythmias, electrocardiographic changes of the hypoxic type, anginal attacks, sudden unexpected death, subendocardial disseminated micronecroses (sometimes confluent into larger nontransmural infarctions), myocardial fibrosis, and acute or chronic congestive heart failure with or without pulmonary edema.

Experimental and clinical evidence has made it clear beyond reasonable doubt that cerebral cortical and subcortical emotional and sensory stimuli, particularly anxiety and anger, elevate the sympathetic tone and thus initiate the local liberation of norepinephrine within the myocardium and epinephrine from the adrenal medulla. Both of these catecholamines augment myocardial oxygen consumption. In the absence of adequate compensatory dilatability of the coronary arteries or in the case of exhaustion of even the normal coronary reserve,[illegible] injurious anoxia will occur in the most directly affected cell groups of the heart muscle, notably in the hemodynamically compressed subendocardium. Emotionally triggered simultaneous rises in peripheral vascular resistance are apt to impose an additional mechanical load on an already metabolically handicapped myocardium.

A still inadequately explored but presumably highly important role of involvement of the adrenal cortex in emotion- and sensory stress-induced myocardial pathology is emerging from recent studies. These have revealed a striking parallelism between the central nervous regulation of adrenergic catecholamine liberation and the secretion of 17-hydroxycorticosteroids and other steroids from the adrenal cortex. In view of the marked intensification of catecholamine cardiotoxicity by adrenal corticoids[illegible] and of the simultaneous overproduction of both myocardial hypoxiating catecholamines and myocardial potassium depleting[illegible] corticoids under emotional stress[illegible] (Fig. 9), further investigation of this challenging problem of cardiac pathogenicity appears to be most promising. (Interestingly, in contrast to emotional arousal, the even more marked sympathetic stimulation during physical exercise is not associated with an increased secretion of adrenal corticoids and accordingly seems to be less cardiotoxic.)

The common denominator of cardiotoxic catecholamine and corticoid action in myocardial metabolism is to be sought in the specific mutually aggravating influences exerted by both of these hormone categories upon local potassium and sodium exchange.

DEGREES of LESION — No. of specimens

A FL CORTISOL + RESTRAINT — 27
B SAME + DIBENZYLINE — 8
C SAME + CHLORPROMAZINE — 18
D SAME + GUANETHIDINE — 9
E SAME + RESERPINE (1 wk) — 16
F SAME + RESERPINE (2 wks) — 8
G SAME + MECAMYLAMINE — 19
H SAME + RESERPINE + MECAMYLAMINE — 15

Fig *10* Degree of stress plus corticoid induced myocardial necroses in rats (*black bars*) reduced by antiadrenergic premedication (From Raab et al American Journal of Cardiology 8 203 1961 by permission )

Whether and to what extent emotional and sensory stress factors have a part in coronary atherogenesis possibly by way of raising the serum cholesterol level remains a moot question

The logical therapeutic approach to clinical cardiac manifestations of at least partially emotional origin consists apart from frank psychotherapy in a reduction of exogenous emotion and sensory induced central stimuli (with tranquilizers hypnotics) and/or the use of peripherally acting antiadrenergic medication (ganglionic blockers catecholamine desensitizing thyrostatic agents beta receptor blockers catecholamine depletors and adrenolytic drugs) (Fig 10)

Early pre morbid prevention is theoretically and practically feasible by the adoption of a serene not overly competitive outlook on life problems choice of a physically and emotionally appealing environment at least periodically and a creative subjectively satisfying utilization of leisure time

However it is imperative to keep in mind that in the same way in which degenerative hypoxic heart disease is pluricausal and not attributable to one single category of pathogenic factors prevention must be carried out equally pluridirectionally

In a somewhat simplified fashion it has to be aimed at (a) diet promoted coronary vascular disease and (b) the exaggerated neurogenic metabolic vulnerability of the myocardium which is caused by the adrenergic triad of jointly or singly contributing lack of exercise tobacco smoking and emotional plus sensory stresses in varying distributions and degrees

## XI Summary

In the complex but increasingly perceptible pluricausal pathogenesis of degenerative (so called coronary ) disease of the heart muscle emotional and sensory stresses play a prominent even though usually only contributory role

Scrutiny of the pertinent contemporary transdisciplinary world literature provides abundant experimental and clinical evidence for a potentially cardiotoxic over production of sympathogenic catecholamines and adrenocortical steroids resulting from emotional and sensory stress induced stimulations of the central nervous system and the pituitary gland

Fear anger and frustration as well as to a lesser extent optical acoustical and thermal annoyances act as the most common potentially pathogenic stimuli

These stimuli disturb via the sympatho adrenomedullary system the oxygen economy of the myocardium (particularly in conjunction with predisposing coronary

atherosclerosis and with the often associated additional adrenergic manifestations of physical inactivity and of nicotine). Intramyocardial electrolyte shifts due to catecholamine induced local hypoxia and superimposed corticoid induced depletion of myocardial potassium may be assumed to constitute the most fundamental metabolic derangements involved.

There is only sparse evidence in favor of a significant contribution of emotional and sensory stimuli to coronary atherogenesis. However, stress induced sympathetic and adrenal cortical overaction seems to affect the myocardium also indirectly by way of elevations of blood pressure and resulting hemodynamic strain.

Prevention and counteraction of emotional and sensory detriments to the myocardium are feasible through psychotherapy, environmental adjustments, physical reconditioning, and tranquilizing and/or directly antiadrenergic medication.

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# Appraisal and reappraisal of cardiac therapy

**Edited by Arthur C DeGraff and Alan F Lyon**

## Reappraisal of digitalis Part II
## Hemodynamic effects of the cardiac glycosides

*Alan F Lyon MD*
*Arthur C DeGraff MD***
*New York N Y*

That digitalis can produce marked improvement in some patients with congestive heart failure is a well known fact There is however disagreement as to the particular situations in which it is most effective Is it as effective in the presence of normal sinus rhythm as with atrial fibrillation? Is it equally effective in heart disease of all etiologies? Does it have any effect in the presence of compensated heart disease or in the normal heart? Furthermore there has been confusion as to the mode of action of digitalis in heart failure It has been variously proposed that it exerts its effect by a direct diuretic action on the kidney by a reduction in the venous return to the heart or by an increase in the force of contraction of heart muscle In recent years the development of cardiac catheterization and other modern recording techniques has led to the resolution of many although not all of the problems

*Range of effectiveness* It is now clear that in most patients with congestive heart failure digitalis will lead to a reduction in mean atrial pressures and in ventricular end diastolic pressures to a rise in cardiac output diuresis and clinical improvement whether the patient is in atrial fibrillation or normal sinus rhythm Although this effect is most striking in the low output failure of arteriosclerotic hypertensive and aortic valvular disease the drug has been demonstrated to be effective in mitral valvular disease pulmonary heart disease and primary myocardial disease and even active rheumatic carditis in which case its value had often been doubted on clinical ground It has also been shown that there are patients apparently similar to those in whom digitalis is markedly effective in whom digitalis has little effect on cardiac pressures and output or in whom it can accomplish no more than diuretic therapy How these patients differ from the larger group is still not clear

*Effect on contractility* The most important factor in the improvement of heart failure is an increase in the contractility of heart muscle that is an increase in both the speed and force of cardiac contraction Direct proof of this increase in the force of cardiac contraction has been obtained not only in isolated heart muscle preparations but also in human subjects In the latter instance this has been demonstrated by the use at open heart surgery of the Walton Brodie strain gauge arch which can record isometric tension in an exposed portion of the beat

Received for publication July 11 1966
*Chief Cardiology Section [illegible] Administration Hospital B[illegible] N Y
**Professor of Therapeutics, New York University College of Medicine and Chief, Cardiology Section, Veterans Administration Hospital, Bronx, N Y

ing heart. This technique has consistently shown the development of an increase in tension after digitalis, whereas the more indirect analysis using the relationship of ventricular end-diastolic pressure and stroke work has not always done so, probably because of compensatory reduction in sympathetic tone.

The other aspect of contractility, the speed of contraction, can be assessed by the rate of rise in ventricular pressure. This is most accurately measured as the first derivative of the first portion of the ventricular pressure curve (dp/dt). This measurement is markedly increased after the administration of digitalis, which gives further evidence of the favorable effect of digitalis on contractility.

It is this increase in contractility that leads to more complete emptying of the ventricles, clearing of venous congestion, fall in venous pressure, and increased cardiac output. This action is adequate to account for most of the effects of digitalis in heart failure, but the total effect of digitalis is more complicated.

*Effects on venous circulation.* It appears that there is an independent and substantial effect of digitalis on the venous bed which leads, both in animals and in man, to a reduction in venous return. This, along with improved ventricular function, contribute to the observed fall in central venous pressure.

Measurements of venous pressure-volume in the forearm and in the splanchnic bed suggest that the effect of digitalis is one of venoconstriction. In the dog, the fall in venous return despite increased venous tone is explained by constriction of the hepatic veins which dams blood in the portal circulation and raises portal pressure. In man, constriction of the hepatic veins does not appear to be adequate to explain the diminished venous return that does occur, and the exact mechanism is unknown.

*Effect on diuresis.* A renal action of digitalis has been demonstrated experimentally. Digitalis inhibits the renal reabsorption of sodium, probably by the same mechanism by which it interferes with the transfer of sodium and potassium in cardiac cells; this effect is quantitatively unimportant at therapeutic levels. Digitalis does cause a diuresis, but it does so by improving primarily cardiac and secondarily renal function. Significant diuresis can occur before there is a clear-cut increase in renal blood flow or glomerular filtration, but these are not the only factors affecting renal function in heart failure. It is likely that this early diuresis is due to a change in some other aspect of congestive heart failure, perhaps hormonal, rather than to a direct effect of the drug on the kidney.

*Effect on the normal heart.* It was suggested in the past that digitalis might be deleterious to the mechanical function of the normal heart. It has been noted that there was often a reduction in the size of the normal heart after digitalis therapy, and it was postulated that, by increasing ventricular tone, digitalis reduced the capacity of the ventricle and thus the cardiac output. More recent studies have shown a variable effect of digitalis on the output of the normal heart; some investigators find no change and others find a slight reduction in cardiac output. This reduction in resting output, if it is present, would appear to be of little significance since the response to exercise is unchanged from the normal. Most important, the increase in force and speed of contraction that digitalis induces in a heart in congestive failure also occurs in the normal heart. Such an increase in contractility is of no importance in the normal subject, in whom the base-line contractility function of the heart is adequate to handle the blood returned to it. When a fall in basal cardiac output does occur in a normal subject given digitalis, it can be attributed to a reduction in venous return produced by the same mechanisms operative in the situation of congestive heart failure.

*Effect on peripheral arteries.* Digitalization produces a rise in peripheral resistance due to arteriolar constriction. The effect in the normal subject is more easily demonstrated than in the presence of congestive heart failure, which itself causes a rise in peripheral resistance. As digitalis relieves congestive heart failure, the stimulus to constriction is reduced, and the net effect is often one of arteriolar dilatation, opposite to the direct effect of digitalis. The direct effect of digitalis on the arteriolar bed is

a local one since it can be demonstrated to occur despite ganglionic blockade and with local perfusion

Just as digitalis can increase the contractility of the normal heart so it can increase the contractility of the hypertrophied heart without failure Such an increase in contractility is of no value to the normal subject whether it is of value to patients with compensated heart disease is in doubt In such patients the usual indices of pressures and outputs at rest and exercise are not modified It has been reported however that the oxygen debt accumulated by such subjects on exercise is reduced Animals whose ventricles are stressed by aortic constriction develop less hypertrophy when they are maintained on digitalis Because of the multiple and complex effects of digitalis in addition to that on contractility the usefulness of digitalis in compensated heart disease must at present be decided on clinical rather than hemodynamic grounds

The major effect of digitalis in heart failure is on contractility Measurement of contractility by strain gauge dp/dt and more indirect measures such as shortening of the rate corrected systolic ejection time and shortening of isovolumic contraction (the period from the onset of contraction to the opening of the semilunar valves) has shown that the effect of digitalis on contractility is not all or none but stepwise Increasing doses of digitalis up to a point will produce increasing augmentation of contractility This observation has important bearing on the traditional concepts of the loading and maintenance doses of digitalis

*Summary* The administration of the cardiac glycosides will result in a reduction in filling pressures increase in cardiac output diuresis and symptomatic improvement in most patients in congestive heart failure irrespective of cardiac rhythm Although they exert direct effects on the peripheral arterial and venous bed and on kidney function the improvement in heart failure that the cardiac glycosides produce is due primarily to an increase in contractility of ventricular muscle The degree of increase in contractility is related to dosage in the therapeutic range

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serum cholesterol during the acute attack. They found it difficult to interpret these findings.

To date no satisfactory explanation of the pathogenesis of acute gouty arthritis has been offered. Wolfson and Robinson have suggested that the acute attack of gout is principally of vascular origin. The decrease in serum cholesterol as well as in serum uric acid during the acute attack may be the result of deposition of these substances in the vascular wall, or they may be utilized in the formation of atheroma.

The occurrence of cerebral infarction and acute gout cannot be accepted as concrete evidence of a causal relation, but the consideration of such a possibility seems to be justified. An attractive postulate for the occurrence of the two disorders in the same individual seems to be that cerebral infarction and gout may be manifestations of the same basic metabolic state in which the cardinal feature is hyperuricemia.

The fundamental problems of cerebral infarction are those of atherosclerosis. Despite the vigorous and prolific efforts that have gone into the study of atherosclerosis during the 50 years since Anitschkow succeeded in producing atherosclerosis in cholesterol-fed rabbits, we know very little about the etiology and pathogenesis of atherosclerosis. Evidence accumulating that atherosclerosis represents a metabolic disorder involving particular lipids, but a final proof of a causal relationship has so far not yet been established. It is possible that hypercholesterolemia as well as atherosclerosis may represent manifestations of an altered metabolic state.

The association of gout and arteriosclerosis has been a clinical concept since the end of the last century. Roberts declared the importance of the uric acid diathesis for the development of thromboembolic phenomena, and Huchard[11] wrote: "Les artério-sclérose et l'atherome vasculaire peuvent être chez certains sujets les seules manifestations de cette diathèse." The subject of gout was forgotten or dropped in the beginning of this century,[?] and the association of gout and arteriosclerosis faded away. Although gout is a malady fairly entitled to boast of its great antiquity, it is apt to be one of the last thought of by the clinician.

The evidence that uric acid has a deleterious effect on the arteries is mainly as follows:

1. During the last decade occasional interest was expressed concerning hyperuricemia in degenerative vascular lesions. A positive correlation between hyperuricemia and coronary artery disease was documented ... and Kramer and associates found hyperuricemia in 3.4 per cent of 351 patients with peripheral vascular disorder. The degree of involvement ... med to be related to the degree of elevation of uric acid.

In a series of 53 cases of cerebrovascular disease there were 19 (3? per cent) in which hyperuricemia was present. The authors discussed the possibility that the elevated level of serum uric acid were the result of cerebral infarction rather than its cause because ... of the 19 patients had recent cerebral infarction and ... additional 5 had a previous history of long-standing gout.

In a survey of serum uric acid in 66 males and 49 females with acute cerebral infarction, hyperuricemia was found in 17 males and 4 females (36 per cent).[13] None of the patients had prior to the analyses of uric acid received drugs with hyperuricemic properties. All of the determinations of uric acid were carried out with enzymatic spectrophotometry developed by Kalckar, Praetorius and Praetorius and Poulsen.[14] Six of the patients had a previous history of gout. It seems to be unlikely that the observed elevation of serum uric acid is related to the presence of stress, to renal failure, or to an abnormal cellular breakdown. A follow-up examination averaging 13 months after the initial stroke revealed hyperuricemia in 15 (34 per cent) of the 64 patients examined, despite the fact that some of the patients had been receiving treatment with uricosuric drugs.

These studies support the clinical impression of a relationship between gout and atherosclerotic disorders.

2. There is a bulk of evidence of a relationship between the metabolism of purines and that of lipids. Since Hutchinson in 1889 in the Clinical Society of London related a case of xanthelasma and gout in a 44-year-old Hebrew, there have been several reports concerning the occurrence of hyperuricemia and hypercholesterolemia. High level of serum uric acid are frequently encountered in essential hypercholesterolemia, and conversely a high level of plasma cholesterol is often found in patients with gout. The reader is referred to a review of the literature concerning this subject.

In my series of 115 patients with cerebral infarction, 14 patients revealed hyperuricemia as well as hypercholesterolemia. The value 3.2 Gm. per liter is taken as the upper limit of normal of cholesterol (unpublished).

Further evidence of a metabolic relationship between blood cholesterol and uric acid was demonstrated by Eadl... who found that blood cholesterol was strikingly lowered by ... A decrease in blood cholesterol has also been observed after the administration of ... Both the drugs have uricosuric effect.

It is established that ... high fat result in an increase in uric ... the blood and decreased amount of the substance ... the urine ... gouty and normal subjects.

3. The report of T... and associates on specific vascular lesions in ? patients with gout supports further the hypothesis of atherogenic effect of uric acid. So does the observation of Osler, who from his wide autopsy and clinical experience noted the frequency of arteriosclerosis and cardiac hypertrophy in gouty persons. He ... ted that nutritional disorders with which excess of uric acid is associated induce in time increased tension, arteriosclerosis, chronic interstitial nephritis and changes in the myocardium.

4. Sey... the an... ses showed that patients with gout had increased bone marrow activity in terms of platelet turnover and great platelet adhesiveness and plasma ... activity ... atherosclerosis. Interestingly, platelet ... al ...

longed and platelet turnover decreased during sulfinpyrazone (Anturan) therapy. There was a corresponding fall in platelet count and decrease in platelet adhesiveness.

The predominance of females over males in the study concerning uric acid values in acute cerebral infarction appears to be telling against the atherogenic effect of hyperuricemia and gout, because of the rarity of gout in women. It seems to be trivial but nevertheless important to emphasize that gout and hyperuricemia are not interchangeable terms. Only 20 per cent of individuals with hyperuricemia will develop articular symptoms. The rarity of gout in females does not exclude nongouty hyperuricemia in this sex.

The frequent occurrence of hyperuricemia and degenerative vascular disease in the same individual does not prove a causal relationship but does appear to be more than mere coincidence. An exact interpretation of this finding cannot be offered. It may be postulated that hyperuricemia, hypercholesterolemia, and atherosclerosis represent manifestations of the same metabolic state. Hyperuricemia will cause clinical gout in those disposed by heredity, and it is suggested that vascular phenomena account for the acute attack of gout.

This hypothesis raises important questions: Does treatment with uricosuric drugs prevent atherosclerosis in hyperuricemic individuals? Is the potent uricosuric effect of certain anticoagulants[26] of any therapeutic significance in individuals with hyperuricemia and atherosclerotic manifestations, and is the effect of Anturan on platelet economy of any importance in preventing the development of thrombosis in gouty subjects? Above all, the incidence of atherosclerotic lesions in patients with gout remains to be determined.

*Ole Ewald Hansen, M.D.*
*Department of Neurology*
*Copenhagen County Hospital*
*Glostrup, Denmark*

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demanded it of us, and so we go on vying with each other for incunabula opulence (see for example the figures on books published by Oxford, Cambridge, and Berkeley academics in the Franks report 1966).

Those who decry must also expound, and it would be mischievous to criticize without attempting to point the way to better things. The fault lies not so much in the concept of the textbook but in our misinterpretation of it as more than a personal expression or analysis of a body of fact. If it remains the latter, as distinct from an attempt to become a means of covering a subject totally and permanently, then it can still be a living and dynamic thing; if it is merely to be a card index, then it would be better stored in a computer or written as a dictionary or encyclopedia. Unfortunately, textbooks and the textbook style have degenerated since Winslow published in 1732 his Exposition of Anatomy, which set a standard of clarity and verbal economy that swept away the fog of overornamented discourse and avoided constructions which, to use his own word, might have been most pleasing to a reader of a light and classical taste. There seems unfortunately to be a return to such elaborate and decorative prose, perhaps because the study of language as a means of communication is passing into too self-conscious a phase.

If we must fly from the turgidity and inadequacy of textbooks and search for better means of expressing ourselves in an engaging manner, we must not forget that other things, such as the free exchange of information, may also be lost. The dissemination of information is reverting strangely enough to the Renaissance situation of personal exchange of views between coteries of savants. In cosmology, immunology, nephrology, and doubtless cardiology, ideas are now exchanged through conferences, the circulation of papers, and advance notices of publication. Although this is in a way admirable, it also has its dangers: first, the possibility of a reductio ad absurdum situation in which one is so well informed of everyone else's work as to be quite inhibited from doing any oneself; secondly, the serious risks of transcribing and transmitting degeneracy as manuscripts whirl around the world and are summarized, abstracted, and misquoted; thirdly, the further multiplication of both papers and journals for facts rather than ideas. Thus, these new societies in close but restricted personal communication are but a partial solution and a danger in that they do not provide for the uninitiated or give rise to a service to learning or to learners. More may be achieved by the periodic narrowly directed conference which has as its prime objective the adoption of certain ideas, concepts, or definitions. Our new textbooks may thus come to be written by consensus and as reports of such gatherings. They need not consequently be cameldrin, as indeed the relatively fiery proceedings of one such recent meeting show. It will, I believe, be increasingly the task of Societies, Institutions, and Journals, such as the AMERICAN HEART JOURNAL, to work out such transiently authoritative but living statements of learning, for the textbook is by the nature of events no longer able to provide.

*H. A. F. Dudley, Ch.M., F.R.C.S.E., F.R.A.C.S.*
*Department of Surgery*
*Monash University*
*Victoria, Australia*

Address: Alfred Hospital, Prahran S.1, Victoria, Australia.

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DISEASES OF THE HEART. By Charles K. Friedberg, M.D., ed. 3, Philadelphia, 1966, W. B. Saunders Company. 1,787 pages. Price $22.

Dr. Friedberg rendered an excellent and much needed service to clinical medicine and cardiology when he published the first edition of his book. The third edition indicates this book's success. It continues to present cardiology in a practical clinical manner and at the same time includes the basis of the diseases and associated pathophysiology. A fairly complete bibliography is appended to each chapter thus making the book a good reference source. The increased size of the book reflects the growth of knowledge in the field of cardiology. This is a good, clearly written book which should be owned by all cardiologists and internists who do a major practice in cardiology. Dr. Friedberg has managed extremely well in keeping his excellent book up to date.

CURRENT DIAGNOSIS. Edited by Howard F. Conn, M.D., Robert J. Clohecy, M.D., and Rex B. Conn, Jr., M.D. Philadelphia, 1966, W. B. Saunders Company. 843 pages. Price $19.

This book is a companion to the excellent and successful *Current Therapy*, which is edited and issued each year. This new book is a very good reference work as well as textbook on the subject of diagnosis. The fields covered are extensive and include among many others: infectious diseases, diseases of the respiratory system, the cardiovascular system, blood and blood-forming organs, the digestive system, urogenital tract, skin, nervous system, and disorders of metabolism, newborn infants, and children. The authors selected to write the many chapters are able clinicians who therefore have presented the data for the practicing physician and the student learning medicine. The presentations are brief and lucid. This reference book will be appreciated by many doctors, and especially those with a busy practice.

## Books received

THE AETIOLOGY OF COMPRESSED AIR INTOXICATION AND INERT GAS NARCOSIS. By P. B. Bennett. New York, 1966, Pergamon Press, Inc. 116 pages. Price $6.

CHRONIC DISEASES AND PUBLIC HEALTH. Edited by Abraham M. Lilienfeld and Alice J. Gifford. Baltimore, 1966, Johns Hopkins University Press. 846 pages. Price $15.

FINE NEEDLE ASPIRATION BIOPSY. By Nils Soderstrom. New York, 1966, Grune & Stratton, Inc. 159 pages. Price $16.

VENTILATION, BLOOD FLOW, AND GAS EXCHANGE. By John B. West. Philadelphia, 1966, F. A. Davis Company. 117 pages. Price $4.

MODERN TREATMENT. Vol. 3, No. 3, May, 1966. 1. Treatment of Alcoholism by Marvin A. Block, M.D. 2. Treatment of Arteriosclerotic Heart Disease by Arthur C. DeGraff, M.D. and Solomon Finch, M.D., Ph.D. New York, 1966, Hoeber Medical Division (Harper and Row). 1,500 pages per year. Price $16 per year.

# Announcements

Immediately after the V World Congress of Cardiology in Delhi, India, a Post-Congress Session will be held in Bombay on Nov. 7 and 8, 1966. The theme of this scientific session will be "Modern Trends in Cardiac Management." The transactions will be in English and the conference will consist of lectures, seminars, and panel discussions.

Delegates wishing to attend the Post-Congress Session in Bombay should contact Dr. Ivan J. Pinto, Organizing Secretary, Esperance, Cumballa Causeway, Bombay 1, India.

A SEMINAR ON DIGITALIS AND THE HEART will be presented Oct. 15 and 16, 1966, at the DeGoesbriand Memorial Hospital, Burlington, Vt., sponsored by the Vermont Heart Association and the University of Vermont in collaboration with the American College of Cardiology. Programs may be obtained from Eugene Lepeschkin, M.D., Cardiovascular Research Unit, DeGoesbriand Memorial Hospital, Burlington, Vt.

# American Heart Journal

*November 1966 Volume 72 Number 5*

## Editorial

### The fallacy of the Bainbridge reflex

*C. L. Patkak, M.B., B.S., M.D., Ph.D. (Glas.)**
*Udaipur, India*

The reflex regulation of the cardiovascular system is well known. These reflexes arise mainly from various sensing structures (sensory receptors) located in the cardiovascular system itself.[1,2] The pressure receptors located in the carotid sinus and aortic arch and at other sites in the arterial tree play the main role in the homeostatic control of blood pressure and cardiac action. Besides the reflexes arising from the extracardiac baroreceptors and chemoreceptors, there is an important group of reflexes originating from the heart itself. Among these reflexes one of the *commonly accepted reactions has been the* Bainbridge reflex, or right atrial reflex, which has been receiving the attention of authors of various textbooks of physiology. As Philip Bard[3] says, this reflex is better known to medical students than any other circulatory reflex. It has been considered to be an important cardiovascular homeostatic mechanism responsible for the regulation of heart rate.

Professor Bainbridge conducted his experiments on anesthetized dogs and showed that intravenous infusions of saline or blood resulted in an increase in the heart rate. This infusion acceleration response was found to be reduced by atropine and abolished by vagotomy. The conclusion was that the infusion raises the intra-atrial pressure and stimulates some stretch receptors from which nervous impulses ascend to the medullary centers where they lead to a reduction in tone of the vagus and also presumably influence the heart rate by simultaneously stimulating the cardioaccelerator center.[4] Thus, the increase in the heart rate was attributed to readjustments in the autonomic activity reflexly through the medullary centers. This infusion acceleration response was called "Bainbridge reflex."

During the past 50 years a number of workers using various *techniques have* investigated this reflex. The universality of infusion acceleration response has not been confirmed nor has any evidence of its being a reflex effect been forthcoming.

DeGraff and Sande[11] noted acceleration in only 50 per cent of cases, but vagotomy was not always effective in abolishing the reflex. Anrep and Segall[5] obtained acceleration frequently but not always in innervated heart lung preparation. They suggested that it was premature to consider an increase in the central venous pressure as the stimulus for the reflex. Ballin and Katz[6] did not induce acceleration in anesthetized dogs, but in unanesthetized dogs they could induce acceleration when either

Received for publication Feb. 10, 1966.
*Department of Physiology, R. N. T. Medical College, Udaipur (Rajasthan), India.

DISEASES OF THE HEART By Charles K. Friedberg M.D. ed 3 Philadelphia 1966 W. B. Saunders Company 1,78 pages Price $72

Dr Friedberg rendered an excellent and much needed service to clinical medicine and cardiology when he published the first edition of his book. The third edition indicates this book's success. It continues to present cardiology in a practical clinical manner and at the same time includes the basis of the disease and associated pathophysiology. A further complete bibliography is appended to each chapter thus making the book a good reference source. The increased size of the book reflects the growth of knowledge in the field of cardiology. This is a good, clearly written book which should be owned by all cardiologists and internists who do a major practice in cardiology. Dr Friedberg has managed extremely well in keeping his excellent book up to date.

CURRENT DIAGNOSIS Edited by Howard F. Conn M.D. Robert J. Clohecy M.D. and Rex B. Conn Jr M.D. Philadelphia 1966 W. B. Saunders Company 843 pages Price $19

This book is a companion to the excellent and successful *Current Therapy* which is edited and issued each year. This new book is a very good reference work as well as textbook on the subject of diagnosis. The fields covered are extensive and include among many others infectious diseases, diseases of the respiratory system, the cardiovascular system, blood and blood forming organs, the digestive system, urogenital tract, skin, nervous system and disorders of metabolism, newborn infant and children. The authors selected to write the many chapters are able clinicians who therefore have presented this data for the practicing physician and the student learning medicine. The presentations are brief and lucid. This reference book will be appreciated by many doctors and especially those with a busy practice.

## Books received

THE AETIOLOGY OF COMPRESSED AIR INTOXICATION AND INERT GAS NARCOSIS By P. B. Bennett New York 1966 Pergamon Press Inc. 116 pages Price $6

CHRONIC DISEASES AND PUBLIC HEALTH Edited by Abraham M. Lilienfeld and Alice J. Gifford Baltimore 1966 Johns Hopkins University Press 846 pages Price $15

FINE NEEDLE ASPIRATION BIOPSY By Nils Soderstrom New York 1966 Grune & Stratton Inc 139 pages Price $16

VENTILATION, BLOOD FLOW AND GAS EXCHANGE By John B. West Philadelphia 1966 F. A. Davis Company 117 pages Price $4

MODERN TREATMENT Vol 3 No 3 May 1966 A Treatment of Alcoholism by Marvin A. Block M.D. *B* Treatment of Arteriosclerotic Heart Disease by Arthur C. DeGraff M.D. and Solomon Fisch M.D. Ph.D. New York 1966 Hoeber Medical Division (Harper and Row) 1,300 pages per year Price $16 per year

# Announcements

Immediately after the V World Congress of Cardiology in Delhi India a Post Congress Session will be held in Bombay on Nov 7 and 8 1966. The theme of this scientific session will be Modern Trends in Cardiac Management. The transactions will be in English and the conference will consist of lectures, seminars and panel discussions.

Delegates wishing to attend the Post Congress Session in Bombay should contact Dr. Ivan J. Pinto Organizing Secretary Esperance Colaba Causeway Bombay 1 India

A SEMINAR ON DIGITALIS AND THE HEART will be presented Oct 15 and 16 1966 at the DeGoesbriand Memorial Hospital Burlington Vt sponsored by the Vermont Heart Association and the University of Vermont in collaboration with the American College of Cardiology. Programs may be obtained from Eugen Lepeschkin M.D. Cardiovascular Research Unit DeGoesbriand Memorial Hospital Burlington Vt

of pulmonary deflation receptors has also been established[26] Hypotension and bradycardia follow stimulation of them It must also be admitted that intravenous infusions are likely to increase the cardiac output and blood pressure and the resultant baroceptor activity is likely to increase the vagal tone instead of decreasing it Thus reflex cardiac acceleration if it is to occur must occur despite the presence of such a formidable number of opposing cardiopulmonary reflexes all of which could be brought into action simultaneously by an increase in the venous return

Many other considerations rule out nervous interference in the infusion acceleration response The stretch receptors or the neural pathways believed to be concerned with the Bainbridge reflex have never been demonstrated by any worker although a large number of workers devoted considerable time and effort to isolating the receptors and their nervous connections (Jarisch and Zotterman[14] Aviado and Schmidt[3] Heymans and Neil[12] and many others) Electrophysiologic recordings of single fiber potentials have also failed to demonstrate any such structures or connections[14 1]

The foregoing discussion clearly indicates that the Bainbridge reflex never had any sound basis Acceleration of heart rate is not a constant accompaniment of intravenous infusion In a few instances in which it has been observed no unequivocal evidence has been produced to show that it is a reflex effect In fact one cannot think of a reflex behaving in this fashion i e operative in some animals and not in others and even operative in the same animal in one trial and not in another under the same experimental conditions However an analysis of the work of various investigators yielded the following conclusions

1 There was very little evidence to substantiate the view that the infusion acceleration response had a reflex basis

2 The term Bainbridge reflex persisted in the literature despite many shortcomings because it had been so firmly entrenched in the minds of respectable teachers It is being perpetuated from textbook to textbook by distinguished authors even in recent years frequently with such arguments that it would be a nice thing or with the unfounded hope that better techniques in the future may be useful

3 The infusion acceleration response did occur in some trials in some animals

4 The heart rate might increase or decrease or remain unaltered as a result of intravenous infusion

5 An initial low heart rate was conducive to the production of the infusion acceleration response and vagotomy was frequently effective in abolishing it

6 Some alternative explanation had to be furnished for the occurrence of chronotropic effects when the intra atrial pressure was raised

The real explanation of the greater chances of obtaining the infusion acceleration response when the initial heart rate was low (i e the vagal tone was high) or when the vagi were intact had been furnished by Tuttle[33] as long ago as 1937 Tuttle showed that the cardioacceleratory response to infusion was abolished by vagotomy not because of elimination of the afferent or efferent limb of the Bainbridge reflex but because right vagal section increased the heart rate almost to its maximal level He showed that the infusion acceleration response could be obtained even after vagotomy if the heart rate were slowed by artificial stimulation of the peripheral end of the sectioned right vagus nerve It appears that in the interest of preservation of the concept of the Bainbridge reflex Tuttle's work was completely overlooked and neglected

In an effort to find an alternative explanation for the infusion acceleration response I decided to extend the work on chronotropic changes in isolated hearts A detailed systematically planned study was therefore undertaken on isolated whole hearts and their individual chambers under critically controlled experimental conditions This work on isolated frog whole hearts[22 3] as well as on mammalian hearts consistently confirmed that a progressive rise in the perfusion pressure was associated with a progressive increase in the heart rate up to a certain critical head of pressure beyond which further increase in pressure either produced no change in the heart rate or the heart rate actually decreased The average maximum rise in the heart rate when the

# Clinical communications

## The surdo-cardiac syndrome

### Three new cases of congenital deafness with syncopal attacks and Q-T prolongation in the electrocardiogram

*Anton Jervell, M.D.**
*Rolf Thingstad, M.D.***
*Thor Oistein Endsjo, M.D.****
*Oslo, Norway*

In 1957 Jervell and Lange-Nielsen[1] described 4 siblings in whom deaf-mutism was combined with a peculiar heart disease. The parents, who were not related, and two other children were healthy and had normal hearing. The deaf-mute children, who otherwise seemed to be quite healthy, suffered attacks of fainting; these had occurred between the ages of 3 and 5 years. The attacks were often provoked by exercise or fear. Three of the children had died suddenly at the ages of 4, 5, and 9 years. One of the children is still alive at the age of 15 years.

Clinical and x-ray examinations, which were performed in 3 of the children, revealed no signs of heart disease.

However, electrocardiograms from 3 of the children revealed a marked prolongation of the Q-T interval. In one child a more extensive study showed a further prolongation of the Q-T interval after exercise and quinidine medication, whereas a shortening was observed after atropine and particularly after digitalis. Changes also in the T waves were observed after effort and quinidine medication. Mechanical systole, evaluated by phonocardiography, was not correspondingly lengthened.

None of the causes known to produce prolongation of the Q-T interval could be demonstrated. The blood levels of calcium, phosphorus, and potassium were normal, as were also the basal metabolic rate and the glucose tolerance test.

Autopsy was performed in one case but revealed no gross abnormality of the heart, and the microscopic appearance of the heart muscle was normal.

The conclusion was that the unusual clinical symptoms, the exceptional electrocardiographic findings, and the serious outcome of the illness represented a characteristic syndrome. The condition was supposed to be due to an inborn error of myocardial metabolism, caused by some unknown enzymatic deficiency.

In 1958 Levine and Woodworth[2] described the case of an 8-year-old deaf-mute boy who from the age of 3 years had suffered attacks of fainting, often provoked by fear or exertion. The ECG showed a long Q-T interval with large and often bifurcated T waves. The clinical and x-ray examinations of the heart were normal, and so also were studies of the electrolytes. The boy died suddenly at the age of 13 years. The heart appeared to be perfectly normal at postmortem examination.

In 1964 Fraser, Froggatt, and James[3] in an extensive publication described 9 cases

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[illegible]
[illegible]

(in 6 siblings) of the syndrome which they named the *cardio auditory syndrome* The 9 patients ranged in age from 5 to 19 years and their first attack appeared at ages ranging from 1½ to 12 years Three of the affected children were siblings in one family and 2 in another family Three of the patients died suddenly at ages 3½ 3½ and 14 years A hypochromic anemia was found in the majority of the patients and was suggested as an additional feature of the syndrome

In addition to the aforementioned cases which presented a very typical syndrome 3 other cases are described without deafness but with an otherwise similar clinical and electrocardiographic picture

In 1963 Romano Gemme and Pongiglione[8] described a 3 month-old female infant who had had serious syncopal attacks since the age of 2 months The child had normal hearing and there was no evidence of deaf mutism in the family An ECG recorded during an attack showed ventricular fibrillation Between the attacks the electrocardiogram revealed a marked prolongation of the Q T interval and broad diphasic T waves In addition ventricular extrasystoles with a very short coupling were registered Two brothers with identical clinical symptoms had died at the ages of 44 days and 4 months

In 1964 Ward[7] described a new familial cardiac syndrome in children Two siblings a girl and a boy had had episodes of loss of consciousness from the ages of 16 and 15 months respectively Both children had normal hearing The boy died during an attack and the autopsy revealed no gross abnormality of the heart Electrocardiograms at rest from both siblings showed an extreme prolongation of the Q T interval The ECG recorded during an attack showed ventricular fibrillation partly of the low voltage and partly of the high voltage type

Examination of the relatives revealed that a 6-year-old brother and the father had quite normal electrocardiograms The mother s ECG however showed a Q T interval which was definitely prolonged as compared with normal values calculated from the usual formula The mother had never had any clinical symptoms herself There was however a history of sudden death in the mother s family

Three additional cases of what we prefer to call the *surdo cardiac syndrome* are now reported They demonstrate a typical clinical picture as well as electrocardiographic signs Two of the children are girls 13 and 10 years old and the third is a 7 year-old boy They had their first attacks at the ages of 9 and 4 years and 2½ months respectively The children are not related

Table 1 *Clinical features of the published cases*

| Case | Author | Sex | Age at onset of fainting attack | Age at death |
|---|---|---|---|---|
| 1 | Jervell and Lange Nielsen 1957 | M | [illegible] | [illegible] |
| 2 | | F | 5 yr | [illegible] |
| 3 | | F | 5 | |
| 4 | | F | 3 y | [illegible] |
| 5 | [illegible] and Woodworth 1958 | M | 3 yr | [illegible] |
| 6 | Fraser Froggatt and James 1964 | F | Infancy | 14 |
| | | [illegible] | 18 mo | |
| 8 | | F | 12 yr | |
| 9 | | [illegible] | | |
| 10 | | F | 18 m | |
| 11 | | M | Inf | 3½ yr |
| 12 | | M | 2½ yr | 3 yr |
| 13 | | F | | |
| 14 | | [illegible] | 7 yr | |
| 15 | Jervell Thingstad and Endsjø 1966 | F | 9 yr | |
| 16 | | F | 4 yr | |
| 17 | | M | [illegible] | |

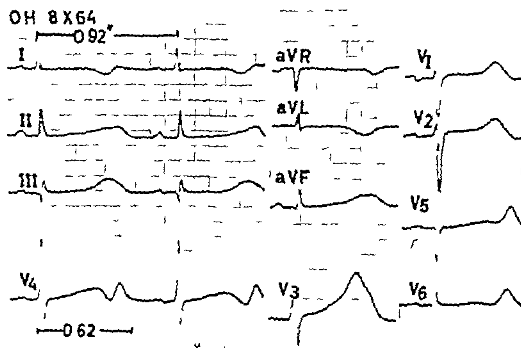



Fig. 1. Case 1. Oddveig H. ECG recorded on Oct. 8, 1964. R-R interval 0.92 sec. Q-T interval 0.62 sec. (upper normal limit 0.40 sec.) ...

Table I presents some of the clinical features in these 3 cases and also in the earlier 14 published cases.

## Case records

*Case 1. Oddveig H., born Aug. 20, 1952.* The parents are not related ... well ... young ... normal hearing. There ... of deaf mutism in the family. The mother had an uncomplicated pregnancy with ... diseases, especially ... rubella, and she had not used any drugs. The delivery was normal.

When the girl was 1½ years old the deafness was discovered. Except for her deaf mutism she has developed quite normally physically ... mentally.

In July 1961, at the age of 9 years, she had her first attack of unconsciousness. She had run about 200 meters to open a gate ... when she suddenly fell to the ground. Her mother, who ... immediately ... found her deathly pale and seemingly lifeless. The lips were ... of the eyes ... The unconsciousness lasted ... about ... minutes. She had ... but she had been incontinent of urine. After the attack ... she ... for ... hours.

During the following 2 years she had ... 7 attacks of unconsciousness ... long lasting as the first. The attacks were provoked by exercise or by anger. Since September 1963 only 1 attack has occurred—in June 1965. This was provoked by swimming and diving. She has otherwise been in good health and has taken part in such exercises as swimming, skating, etc.

In connection with the first attack she underwent neurological examination and an EEG was recorded. Nothing abnormal was found. The diagnosis of epilepsy was supposed, however, and treatment with phenytoin and barbiturate was started, but did not influence her attacks.

Since October 1964 she has been examined several times in the Medical Department, Trondheim Central Hospital. Her general condition has been normal except for the deaf mutism. Audiometry has disclosed an almost complete deafness, and the findings are consistent with the usual findings in congenital deafness.

Cardiological examination has not revealed any signs of organic heart disease. A short systolic murmur (Grade 1-2) was interpreted as being functional. X-ray examination has shown the size and configuration of the heart to be quite normal, the relative volume 450 ml per square meter of body surface. Blood pressure is 100/60 mm Hg.

Treatment with digitoxin was started on ... 3 1965. She was given 0.3 mg of digitoxin for 3 days, ... 0.1 mg daily. For a short period the dose had to be reduced to 0.10 mg and 0.05 mg on alternate days.

The ECG at the first examination on Oct. 8, 1964 was highly abnormal (Fig. 1). The Q-T interval was markedly prolonged, measuring 0.62 sec., whereas the upper normal limit with R-R distance of 0.92 sec. ... 0.40 sec. (Hegglin's formula*). The T waves

*Q-T = ... ... R-R + 0.18 ± 0.04 sec.

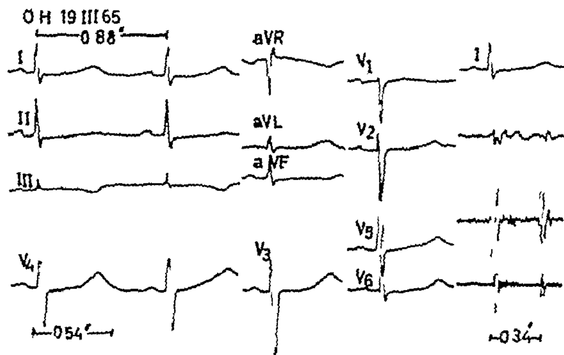



Fig. 3. Case 1. Oddvar H. ECG recorded on March 19, 1965, after vigorous stair running immediately after the ECG in Fig. 2 was taken. R-R interval 0.88 sec. Q-T interval 0.54 sec. (*upper normal limit 0.40 sec.*) Mechanical systole 0.34 sec. and the beginning of the second sound correspond to the middle of the T wave. Electrical systole is prolonged, whereas mechanical systole has normal duration. Also noteworthy is the fact that the ECG shows no *S-T depression in spite of full digitalization*.

pileptic treatment has been tried, but without any result.

Treatment with digitoxin was started on Feb. 3, 1965. She received 0.3 mg. daily for 3 days, then 0.05 mg. daily for 1 week, and later 0.1 and 0.05 mg. on alternate days until March 2. Since then she has taken 0.1 mg. of digitoxin daily. For shorter periods the doses have had to be reduced because of nausea.

Since being placed on digitoxin in March, 1965, she has had only one attack, which occurred once when she became frightened.

Since January, 1965, she has been examined several times at the Medical Department, Trondheim Central Hospital. Except for a slight anemia, her general condition has been good. Audiometry showed an almost complete deafness identical to that usually recorded in cases of congenital deafness.

An examination of the heart disclosed a loud systolic murmur (Grade 3) maximal in the third left intercostal space. The murmur was considered to be functional and related to the anemia. The heart size was normal, and an x-ray study gave a heart volume of 370 ml. per square meter of body surface. Blood pressure was 115/40 mm. Hg.

The electrocardiograms, however, showed very marked abnormalities and with the same pattern as in Case 1. An ECG recorded on Jan. 9, 1965 (Fig. 4) showed a prolonged *Q-T interval of 0.54 sec.* against the upper normal limit of 0.40 sec. (Hjung formula). The T waves were also abnormal, neg-ative in Leads I and aVL and huge with a *bizarre* shape in other leads, especially in Lead $V_4$. After exercise the ECG (Fig. 5) showed prolongation of the Q-T interval to 0.64 sec. (*upper normal limit* 0.41 sec.) and the shape of the T waves were also more abnormal. It was also striking that the heart rate was not accelerated after exercise.

After the patient had been treated for 10 days with digitoxin the ECG was slightly normalized and after 2 months on digitoxin the ECG was almost normal (Fig. 6). The Q-T interval of 0.40 sec. corresponded to the upper normal limit and the beginning of the second heart sound coincided with the end of the T wave. After exercise, however, the Q-T interval was again considerably prolonged in spite of a slower heart rate (Fig. 7). Mechanical systole, on the other hand, was shortened and the beginning of the second heart sound now coincided with the beginning of the T wave. In spite of digitalization to a degree that gave nausea, *no depression of the S-T interval developed*.

The laboratory data were as follows: ESR per 1 hr. = 3 mm. Hemoglobin = 10.3 Gm. per 100 ml. RBC = 4.73 million per cubic milliliter. MCH = 23. Hematocrit = 40. Serum iron = 3 gamma per 100 ml. WBC = 5,800 per cubic milliliter. A blood smear showed slightly hypochromic RBC but was other-*wise normal*.

Serum Cl = 107 mEq. per liter. Serum Na = 140 mEq. per liter. Serum K = 4.4 mEq. per liter. Serum

J S 29 I 65

0 92″

0 54″

Fig 4 Case 2 Janna S ECG recorded on Jan 29 1965 P P interv 1 0 92 [illegible] ec Q T interval 0 34 se (uppe normal limit 0 40 sec ) Abnormal T wa e in several lead

J S 29 I 65

0 94″

0 64″

Fig 5 Case J [illegible] S ECG [illegible] Jan [illegible] 1965 [illegible] running immediately after the ECC Fig 4 was taken [illegible] 0 94 [illegible] Q T inter [illegible] (upper [illegible] 0 41 [illegible] ) After the exercise [illegible] the Q [illegible]

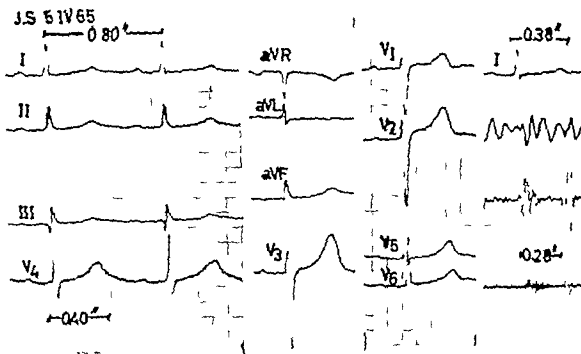



Fig. 8 Case 3 J. n ia S ECG recorded on April 5 1965 after digitoxin medic tion for 2 months The ECG r n l ced R interv 1 0 80 sec Q T terv l 0 40 (upper norm l limit 0 40 sec ) Mechanical systole 0 28 sec nd the beginning of the second sound corresponds to nd of the T w e Showing th t electrical nd mech l s t le are w thin normal limit

C = 9 ( mg pe 100 m l Serum F = 4 6 mg per 100 ml Serum Mg = 2 7 mEq per liter pH = 7 41 J te m m RBC = 91 mEq per liter The urine was normal Serum protein = 7 9 Gm per 100 ml Electrophoresis was normal except for the beta globulins wh h ere slightly increased to 1 7 Gm per 100 ml (14 9 pe cent) EEG and EMG were normal

The labor tory data indicated a slight iron deficiency nemi nd during treatment of the patient w th iron the hemoglobulin rapidly rose to normal v lue

*Case 3 F nd J E b n Sept 5 1957* The mother was 16½ year old t the t me of birth of this child No information w as il ble in regard to the father The mother had attacks of syncope in adolescence There is no case of deaf mutism in her family

When the boy w ? ears old it was realized that he wa deaf Apart from the deaf mutism his development wa sat factory At the age f 2½ months he had his f rst ttack of tonic contr ction and unconscious ness As he grew older he had similar attacks provoked by exercise f ar and anger gen erally about 2 attacks pe year Since the age of 5 years he has experienced a second type of attack usually triggered by exercise but occa sionally by fear and anger During these attacks he becomes very pale cla ps his h nd across h chest men cries v lently and turns ver n h ] with ut l ss f ons ious ess r ing r ntr ction Th

pul e found to be regular and of normal frequency during these attacks Repeated EEG examination ha e revealed no abnormality Nevertheless his condition wa considered to be a form of epilep y and he was treated w th barbiturates and phenytoin without any noticeable effect

Since May 1965 he h s be n examined regul l and ontrolled t the Children Department Ulle vål Ho pital O l His gener l ondition has b en good except for his de f mutism Audiometry h shown complete b l teral deafness Many attack have been observed during his stay in the ho pit l

Cardi logical ex m nation has not re e led ny m f org nic heart d se se A short syst lic mur mur wa interpreted as being fun tional The sh pe nd size f the heart w re norm l the r l tive vol ume wa 320 ml per square meter of body surf Blood pres ure w 110/60 mm Hg

Treatment w th d g t xin w s tarted on M y 21 1965 After saturation the d ily dose w s 0 14 mg f cetyldigitoxin During the short period of l servation afte he w s fully d g talized w h e t f und ny convincing h n e in the umbe r f the sev rity f the ttack

An ECG recorded on May 15 1965 w s highly abnorm l (Fig 8) The Q T interv sh w markedly prolonged me suring 0 ( sec when the upper n rmal limit at R R di t ce 1 10 sec 0 41 sec (Ljung [illegible]

[illegible]

Fig. 7. Case 2. J na S. ECG recorded on April 5, 1965 after cautious stair running immediately after the ECG in Fig. 6 was taken. R-R interval 0.90 sec. Q-T interval 0.54 sec. (upper normal limit 0.40 sec.). Mechanical systole 0.26 sec and the beginning of the first sound corresponds to the beginning of the T wave. Electrical systole is prolonged after exercise, whereas mechanical systole is shortened. In spite of full digitalization no obvious S-T depression has developed.

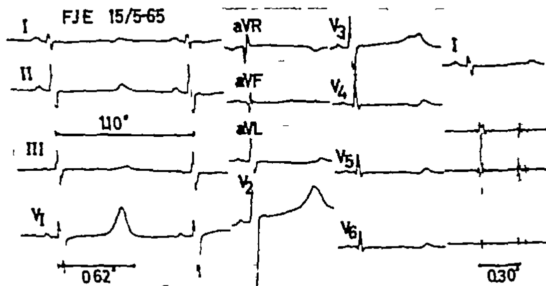



Fig. 8. Case 3. Fred J. F. ECG recorded on May 15, 1965. R-R interval 1.10 sec. Q-T interval 0.62 sec. (upper normal limit 0.41 sec.). Abnormal T waves in several leads. Mechanical systole normal. Distance from first to second heart sound is 0.30 sec.

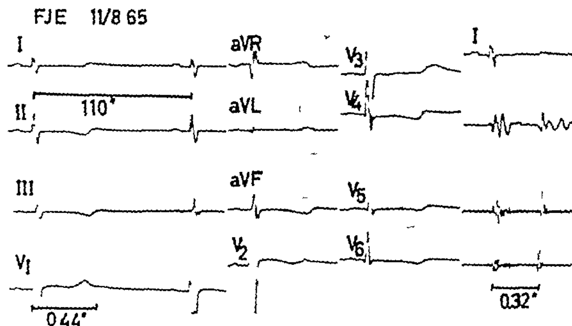



Fig. 9. Case 3. Fred J. E. ECG recorded on Aug. 11, 1965, after digitalis treatment for 3 months. The Q-T c...d normalized. R-R interval 1.10 sec. Q-T interval 0.44 sec. (upper normal limit 0.44 sec.) Mechanical systole normal and the beginning of the first heart sound corresponds to the end of the T wave.

gram showed that the mechanical systole was normal (0.30 sec.) and much shorter than electrical systole (0.?? sec.). After digitalis medication was started the ECG normalized and after 3 months the Q-T ... was normal (Fig. 9), the interval being 0.44 sec., just corresponding to the upper normal limit (Hegglin formula). The boy was at that time fully digitalized with slight symptoms of intoxication.

The following laboratory data were obtained in May, 1965: ESR per 1 hr. = 4 mm. WBC = 5,500 per cubic milliliter. Hemoglobin = 10.5 Gm. per 100 ml. RBC = 5.8 million per cubic milliliter. MCH = 18.

Serum Cl = 110 mEq. per liter. Serum Na = 142 mEq. per liter. Serum K = 4.8 mEq. per liter. Serum Ca = 7.4 mg. per 100 ml. Serum P = 5.2 mg. per 100 ml. Serum Mg = 3.2 mEq. per liter. Potassium in RBC = 103 mEq. per liter. Cholesterol = 200 mg. per 100 ml. PBI = 5 gamma per 100 ml. Serum protein = normal amount, but gamma-globulin reduced to 5 per cent. Immunoelectrophoresis showed hypogammaglobulinemia equally distributed on all three fractions. The serum fatty acids were normal in amounts and distribution. Chromatography of amino acids and sugars in the urine showed normal values. EMG and EEG were normal. Chromosome examination did not show any abnormalities.

The iron-deficiency anemia responded rapidly to iron treatment.

## Discussion

*The attacks.* Fraser and associates[4] have given a very thorough description of the attacks in patients with the surdo-cardiac syndrome. They describe three categories of attacks, viz: episodes without loss of consciousness, those with loss of consciousness and recovery, and those terminating fatally.

Attacks without loss of consciousness occurred in Jervell and Lange-Nielsen's Case 3, in Levine and Woodworth's case, in Fraser and associates' Cases 1, 4, and 5, and in our Case 3. Possibly, such minor attacks may have occurred undetected in other cases. A common feature of these attacks is that the children stop moving, lie down or sit down, and refuse to go further. They grasp their breast or stomach and moan or cry. The pulse is normal during the attacks. After some minutes the attack will be over and the patient will again feel well. The attacks are also provoked by exertion or mental stress. The resemblance to attacks of angina pectoris is obvious. These attacks, however, are certainly not caused by coronary ischemia. The metabolic disturbance may, however, on special occasions, for example after exercise, result in an accumulation of metabolites.

Concerning the attacks with loss of con-

sciousness and eventually death the mechanism is obviously a different one but cannot be determined with certainty until an ECG during such an attack is available The attacks have however the character of Adams Stokes attacks and are probably caused by ventricular fibrillation

*The electrocardiographic findings* The electrocardiographic abnormalities in the three cases described show a striking resemblance to one another as they do also to the findings in the previously published cases Typical is a marked prolongation of the Q T interval The QRS complexes however are of normal appearance and duration The prolongation of the ventricular complex is therefore entirely due to prolongation of the S T interval and T wave A disorder of repolarization corresponding to Phases 2 and 3 must therefore be the underlying cause

As previously observed [4] the appearance of the ECG may change from day to day This is probably explained by the fact that different factors may influence the ECG in these cases It has been shown previously that exercise and quinidine medication prolong the Q T interval whereas atropine and digitalis medication have a shortening influence

In the cases reported here the effect of cautious exercise on the ECG is convincingly demonstrated (Figs 3 5 and 7) In some instances prolongation of the Q T interval after exercise appeared without any change in the heart rate (Fig 5)

After digitoxin medication on the other hand the Q T interval decreased to just below the upper normal limit (Figs 2 6 and 9) Furthermore it is remarkable that digitalization to an extent which provoked clinical signs of intoxication did not produce S T depression

A further characteristic finding is that mechanical systole evaluated by the distance between the first and the second heart sounds is of normal duration in contrast to electrical systole (Figs 3 7 and 8)

The electrocardiograms also show marked abnormalities of the T waves which are partly negative partly bifurcated diphasic or broad and high The T waves also vary in appearance from one examination to another and become more abnormal after exercise whereas they normalize after digitoxin medication Remarkable also is the fact that neither extrasystoles nor other arrhythmias have ever appeared in the numerous electrocardiograms recorded in our patients

The abnormalities in the electrocardiogram resemble those due to hypokalemia but neither in our 3 cases nor in any of the previously published cases has hypokalemia ever been found and the potassium content in red blood cells was also normal Nor have any other electrolyte disturbances been recorded Therefore a biochemical explanation for the ECG abnormalities cannot be given Possibly the membrane permeability for electrolytes is affected due to some inborn enzymatic deficiency

*Postmortem findings* Autopsy has been performed in 5 cases In 3 of them (Jervell and Lange Nielsen's Case 1 Levine and Woodworth's case and Fraser and associates Case 6) there were no convincing pathologic findings on macroscopic and microscopic examination In Fraser and associates Cases 1 and 7 the autopsies were conducted with special reference to the conducting system and they showed consistent abnormalities some compatible with sudden death For details we refer to their original communication[3] (pp 376 377 and 379) Possibly some of their pathologic findings may have been caused by anoxemia during the Adams-Stokes attacks

*Genetic problems* Fraser Froggatt and Murphy[4] have discussed the genetic problems of the surdo-cardiac syndrome They find a high frequency of consanguineous unions among the parents of affected children and they conclude that the data are consistent with a hypothesis of recessive inheritance Those heterozygous for the gene may have slight or moderate prolongation of the Q T interval The syndrome accounts for a small proportion (<1 per cent) of the total number of children with severe educational deafness in the British Isles

In our Cases 1 and 2 there was no consanguinity among the parents In Case 3 the father is not known In all 3 cases we have examined the relatives and in Cases 1 and 2 the clinical and ECG findings were normal in parents as well as in siblings

Concerning Case 3 the mother has a history of attacks of syncope in girlhood but

no details are known. She has, however, no signs of organic heart disease. Her ECG shows a slight prolongation of the Q-T interval (with a R-R distance of 1.00 sec. the Q-T intervals are 0.42 to 0.44 sec., against an upper normal limit of 0.42 sec.). There is, however, no discrepancy between mechanical and electrical systole. After exercise the R-R interval shortened to 0.58 sec. and the Q-T interval to 0.36 sec., against an upper normal limit of 0.33 sec. This means a relative prolongation of the Q-T interval after exercise. However, the relationship between mechanical and electrical systole is normal also after exercise.

We must conclude that our cases do not give any positive information about heredity of the surdo-cardiac syndrome.

*Relationship between abnormal myocardial repolarization and deafness.* Fraser and associates[14] have discussed this problem in detail and they conclude as follows: "It is suggested that the association of congenital deafness with retinitis pigmentosa (Usher's syndrome), with a defect in thyroxine synthesis (Pendred's syndrome), and with a defect in cardiac conduction (a third distinct syndrome) may reflect pleiotropic manifestations of three widely disparate inborn errors of metabolism. The common feature of congenital deafness may be associated with the extreme sensibility of the VIIIth nerve to metabolic disturbances and chemical toxins." To this we have nothing to add, but the problem is of importance for the discussion about the relationship between the surdo-cardiac syndrome and the syndrome described by Romano and associates and by Ward.

*Relationship between the surdo-cardiac syndrome, the syndrome described by Romano and associates and by Ward, and attacks in children of ventricular fibrillation without Q-T prolongation.* The surdo-cardiac syndrome and the syndrome described by Romano and associates and by Ward have in common the appearance of episodes of unconsciousness, also sudden death in some cases, and furthermore prolongation of Q-T in the ECG. But an important difference is the complete congenital deafness which is not found in the cases described by Romano and associates and by Ward. In these latter cases the symptoms also start at a very early age, viz. 7, 16, and 17 months, but children with the surdo-cardiac syndrome have their first attacks later, the majority of them at an age between 3 and 7 years.

It is also worth mentioning that several cases of Adams-Stokes attacks caused by ventricular fibrillation have been described in children without organic heart disease and with a normal Q-T interval in the ECG.[1,8]

Thus three syndromes may be distinguished in children with Adams-Stokes attacks but without signs of organic heart disease: (1) the surdo-cardiac syndrome, (2) the syndrome with prolonged Q-T interval and attacks of ventricular fibrillation but without deafness, and (3) the syndrome with multiple extrasystoles and attacks of ventricular fibrillation, but without deafness and without prolongation of the Q-T interval in the ECG.

*Diagnosis, treatment, and prognosis.* No diagnostic problem will exist if all physicians who care for deaf-mute children are familiar with the syndrome. An ECG will immediately make the diagnosis clear. In many cases, as occurred in our 3 cases, the attacks have been mistaken for epileptic fits, and the patients have for a shorter or longer time been given antiepileptic treatment.

Taking into consideration also the other syndromes mentioned, we recommend that an ECG be registered in all children with a history of fits or attacks of fainting or unconsciousness, and preferably that an ECG be recorded after exercise also.

The importance of a correct diagnosis is evident, because adequate treatment may possibly be life saving, and the patient can be spared ineffective antiepileptic treatment. A correct diagnosis will also be important for prognostic considerations.

In regard to treatment, the following facts are of significance: (1) Because the attacks are usually provoked by exercise, fright, anger, etc., the children, in so far as possible, must be kept away from physical as well as mental stress. (2) Digitalis in adequate doses seems to be indicated. The normalizing effect on the ECG is obvious, as shown in Jervell and Lange-Nielsen's Case 1 and in our 3 cases. In our Case 2 the treatment also had a convincingly favorable effect on the attacks. (3) The symp-

toms seem to lessen as the children get older and complete recovery may be a possibility. This question may be settled by further observation of the affected children.

The prognosis is undoubtedly very grave. Seventeen patients with the surdo-cardiac syndrome have so far been described and 7 of them have died at ages from 3 to 14 years. However, the prognosis may be considerably improved through a closer supervision of the children together with adequate digitalization.

## Conclusion and summary

Three cases of the surdo-cardiac syndrome are described. Since the first publication in 1957[3] 17 cases are now known. The symptoms and signs are very characteristic; the following are the most important: There is congenital deafness with attacks of unconsciousness, probably Adams-Stokes attacks caused by ventricular fibrillation, or milder attacks resembling angina pectoris. The attacks are usually provoked by exercise or mental stress such as fear and anger.

In the ECG a marked prolongation of the Q-T interval is found with abnormal and bizarre T waves. The ECG abnormalities increase considerably after exercise. In contrast, mechanical systole is quite normal and shortens after exercise. Digitalization has a very distinct normalizing effect on the ECG. At least in one case (our Case 2) digitalization also had a beneficial influence on the attacks of unconsciousness.

The cause of the abnormal repolarization phase in the myocardium is supposed to be due to an inborn error of metabolism caused by some enzymatic deficiency which may possibly hamper the transport of electrolytes through the cell membrane.

A similar syndrome with Q-T prolongation and attacks of ventricular fibrillation is described by Romano and associates and by Ward. This syndrome, however, differs from the surdo-cardiac syndrome in the absence of congenital deafness. From a clinical point of view it seems to be better not to confuse the two syndromes.

## Addendum

*Case 3. Fred J. E., born Sept. 5, 19 7.* This patient was re-examined on April 30, 1966, after he had taken acetyldigitoxin 1.14 mg. daily for 11 months. Since October 1965 he has had no attacks of unconsciousness and also he has tolerated physical exercise much better. A further normalization of the ECG was found with a Q-T interval of 0.33 sec.; however, this was again prolonged to 0.44 sec. after exercise, stair running for 1 minute. The exertion obviously induced pains in his chest, since he clasped his hands across his chest and cried. The pains subsided after about 1 minute. In this case, as well as in Case 2, digitoxin apparently has had a favorable effect not only on the appearance of the ECG but also on the attacks of unconsciousness and on the patient's ability to tolerate physical exercise.

We are greatly indebted to Dr. Terje Ba ther, chief physician at the Home for the Deaf, Nor, and to Dr. Erling Esp, physician at the School for Deaf Children in Trondheim, for their valuable help.


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# A comparison of the hemodynamic effects of tachycardia produced by atrial pacing and atropine

*Bernard D. Kosowsky, M.D.**
*Emanuel Stein, M.D.*
*Sun H. Lau, M.D.*
*John B. Lister, M.D.*
*Jacob I. Haft, M.D.*
*Anthony N. Damato, M.D.*
*Staten Island, N. Y.*

Atropine has been used to produce increases in heart rate both clinically and in investigations relating the effects of heart rate to cardiac function. The chronotropic effect of atropine is well established. However, it has not been clearly determined whether atropine affects other cardiovascular parameters. Comparisons between the control and atropine states are difficult to evaluate because it is not clear whether the changes in hemodynamics that may occur are secondary to tachycardia or are manifestations of the vagolytic or direct effects of the drug.

With the use of atrial pacing it is possible to increase the heart rate without significantly altering the hemodynamic state.[1] It is possible, therefore, to study the effects of atropine independently of its chronotropic property by comparing values obtained with atropine to those in the resting state at similar heart rates. The present investigation was designed to compare the hemodynamic effects of tachycardia produced by atrial pacing and by atropine in normal subjects.

## Methods

Investigations were performed in 9 normal male volunteers 23 to 50 years of age during cardiac catheterization. All studies were carried out with the subjects in the supine position in a resting, nonsedated, postabsorptive state.

Through an antecubital vein, a No. 7 or 8 Cournand catheter was positioned in the main pulmonary artery and a No. 5 tripolar electrode catheter was positioned along the lateral wall of the right atrium. A No. 18 Cournand needle was inserted into a brachial artery. Pressures were obtained by means of Statham 23D strain gauges. Cardiac outputs were determined in duplicate by the dye-dilution technique

From the Cardiopulmonary Laboratory, United States Public Health Service Hospital, Staten Island, N. Y.
Supported in part by Research Grant No. CD-00088 [illegible] and [illegible] United States Public Health Service [illegible] Bureau of Medical Services [illegible] Public Health Service [illegible] Grant No. [illegible]
Received for publication [illegible]
[illegible] Heart Disease Control [illegible] Medical Research Center [illegible] 20005

with 7.5 mg. of indocyanine green dye being injected into the pulmonary artery and with blood sampled from the brachial artery through a cuvette densitometer. All recordings were made on an eight channel photographic oscilloscopic recorder. Cardiac outputs were calculated from the inscribed curves using the Stewart-Hamilton formula.

Atrial pacing was accomplished by means of a battery-powered pacer connected to the electrode catheter. The atria were paced at various rates up to 160 beats per minute or until A-V block occurred at a milliamperage of approximately twice threshold. The pacer was not turned off during the intervals between determination.

Mean arterial pressures and mean systolic pressures were planimetrically determined over two respiratory cycles. The systolic ejection time (SET) was derived from the brachial arterial pressure pulse. The tension time index (TTI) was calculated according to the method of Sarnoff and associates.[3] Stroke index (SI), total peripheral resistance (TPR), mean systolic ejection rate (MSER), and left ventricular work index (LVWI) were calculated from the standard formulae.

In each subject, cardiac outputs, electrocardiograms, and arterial pressure tracings were recorded at sinus rhythm and after 3 to 5 minutes of atrial pacing at various heart rates. These studies were repeated 3 minutes after the intravenous injection of 2 mg. of atropine sulfate administered over a 1 minute period.

**Results**

The data from all of the subjects are presented in Table I. Statistical analyses were made on pairs of values *in individual* subjects obtained at similar heart rates (within 10 beats per minute) in the control and atropine states. These values are noted by an asterisk in Table I.

*Cardiac index.* The administration of atropine resulted in no *significant change* in cardiac index ($p > .90$) (Fig. 1). Increasing the heart rate by *means of* atrial pacing did not significantly change the cardiac index, although there appeared to be a slight decrease in cardiac index at the maximum heart rates obtained with and without atropine. The stroke index varied inversely with heart rate and was not affected by atropine at similar heart rates.

*Brachial arterial pressure.* The brachial arterial pressure, mean arterial pressure, and the mean systolic pressure were unchanged by atropine ($p > .50$) or by changes in heart rate.

*Systolic ejection time.* At similar heart rates there was no significant difference between the SET obtained by atropine and that obtained by atrial pacing ($p > .90$) (Fig. 2). Increases in heart rate by atrial pacing resulted in a linear increase in SET with and without atropine.

*Tension time index.* There was no significant difference between the TTI before and that after the administration of atropine at similar heart rates ($p > .30$) (Fig. 3). The TTI increased with heart rate paralleling the changes in SET.

*Total peripheral resistance.* The TPR was not significantly altered by the administration of atropine ($p > .60$) or by changes in heart rate.

*Mean systolic ejection rate.* At similar heart rates the MSER before and that after the administration of atropine were not significantly different ($p > .50$). Under both conditions the MSER varied inversely with heart rate.

*Left ventricular work index.* The LVWI was not altered by atropine ($p > .90$) or by changes in heart rate.

**Discussion**

The effect of atropine on cardiac output has been extensively investigated. Several studies have shown an increase in output after intravenous atropine,[4] although other studies in human beings and dogs failed to show any changes.[7-11] Lancaster and his associates[6] have shown that atropine and rapid atrial pacing both have an immediate effect of increasing cardiac output with a return to control values after a few minutes. In the present study, since the pacer was not turned off between determinations, the effects of acutely changing the heart rate were not evident.

Because of the previous unavailability of similar heart rates without atropine, comparisons of other parameters that might be affected by atropine have not

*Table 1 Hemodynamic data recorded before and after the administration of atropine*

| Patient Age (yr) | HR (per min) | CI (L/min/M²) | SI (ml/M²) | BP (mm Hg) | SPT (sec/min) | TTI (mm Hg sec/min) | TPR (dynes sec cm⁻⁵ M²) | MSER (ml/sec/M²) | LVSWI (Kg M/min/M²) |
|---|---|---|---|---|---|---|---|---|---|
| M I | [illegible] | 2 74 | 4? | 114 | 21 | 2 440 | 3 320 | 130 | 4 25 |
| 50 | 118 | 2 [illegible] | 25 | 110 | 28 | 3 200 | 2 940 | 107 | 4 51 |
| | 144 | 2 71 | 19 | 103 | 30 | 3 300 | 3 040 | 90 | 3 81 |
| | 114 A | 2 91 | 25 | 105 | 28 | 3 050 | 2 900 | 103 | 4 16 |
| | 115 A | 2 92 | 26 | 101 | 28 | 3 100 | 2 850 | 104 | 4 15 |
| | 146 A | 2 [illegible] | 19 | 107 | 32 | 3 400 | 3 110 | 86 | 4 01 |
| C I | 62 | 3 92 | 63 | 70 | 21 | 1 530 | 1 430 | 186 | 3 66 |
| 32 | 77 | 4 01 | 52 | 80 | 23 | 1 800 | 1 560 | 175 | 4 35 |
| | 106 | 5 05 | 48 | 92 | 27 | 2 700 | 1 460 | 184 | 6 29 |
| | 133 | 5 15 | 3? | 92 | 31 | 3 100 | 1 430 | 166 | 6 42 |
| | 160 | 3 [illegible] | 25 | 93 | 32 | 3 200 | 1 880 | 124 | 5 00 |
| | 114 A | 4 70 | 40 | 98 | 28 | 2 900 | 1 660 | 165 | 6 57 |
| | 125 A | 4 35 | 31 | 95 | 31 | 3 250 | 1 760 | 140 | 5 62 |
| | 160 A | 3 [illegible]6 | 24 | 100 | 33 | 3 460 | 2 170 | 114 | 5 12 |
| D D | 70 | 4 70 | 67 | 125 | 2? | 2 875 | 2 120 | 204 | 8 09 |
| 49 | 88 | 4 50 | 51 | 130 | [illegible] | 3 770 | 2 310 | 190 | 8 06 |
| | 11? | 4 40 | 39 | 135 | 29 | 4 200 | 2 450 | 155 | 8 20 |
| | 144 | 3 78 | 27 | 135 | 31 | 4 300 | 2 840 | 123 | 7 23 |
| | 1?5 A | 4 05 | 32 | 135 | 32 | 4 600 | 2 660 | 120 | 7 55 |
| | 130 A | 4 60 | 35 | 135 | 32 | 4 700 | 2 340 | 144 | 8 60 |
| | 145 A | 5 25 | 39 | 130 | 32 | 4 600 | 1 960 | 164 | 9 35 |
| | 155 A | 4 88 | 31 | 135 | 34 | 4 800 | 2 110 | 161 | 8 79 |
| A D | 60 | 3 86 | 64 | 96 | 20 | 1 980 | 1 990 | 194 | 5 04 |
| 23 | 88 | 4 3 | 4? | 100 | 24 | 2 650 | 1 850 | 174 | 5 90 |
| | 96 A | 3 95 | 41 | 100 | 27 | 2 820 | 2 020 | 148 | 5 38 |
| | 10? A | 4 1? | 40 | 100 | 28 | 2 890 | 1 950 | 151 | 5 60 |
| | 136 A | 3 85 | 28 | 97 | 34 | 3 300 | 2 050 | 143 | 5 21 |
| L B | [illegible] | 3 78 | 5 | 100 | 23 | 2 460 | 2 100 | 134 | 5 15 |
| 29 | 114 | 5 10 | 45 | 79 | 30 | 3 180 | 1 370 | 166 | 6 80 |
| | 134 | 4 [illegible]0 | 35 | 95 | 33 | 3 320 | 1 520 | 141 | 6 06 |
| | 154 | 3 8 | 25 | 96 | 34 | 3 400 | 1 980 | 114 | 5 10 |
| | 120 A | 4 47 | 37 | 100 | 30 | 3 190 | 1 780 | 149 | 6 09 |
| | 125 A | 4 36 | 35 | 100 | 31 | 3 220 | 1 830 | 141 | 5 92 |
| | 139 A | 4 70 | 30 | 96 | 35 | 3 410 | 1 630 | 136 | 6 14 |
| N Q | 61 | 3 63 | 60 | 120 | 2 | 2 690 | 2 640 | 169 | 3 98 |
| 45 | 9 | 4 10 | 4 | 112 | 2 | 3 390 | 2 180 | 153 | 6 28 |
| | 121 | 3 63 | 30 | 113 | 30 | 3 300 | 2 410 | 123 | 5 70 |
| | 96 A | 3 49 | 56 | 120 | 26 | 3 700 | 2 740 | 134 | 3 70 |
| | 100 A | 3 58 | 36 | 114 | 26 | 3 250 | 2 520 | 138 | 5 59 |
| | 101 A | 4 11 | 40 | 114 | 27 | 3 330 | 2 270 | 153 | 6 41 |
| | 118 A | 3 43 | 29 | 116 | 35 | 3 520 | [illegible]00 | 122 | 5 45 |
| | 147 A | 3 97 | 2 | 115 | 33 | 4 090 | 2 320 | 119 | 6 18 |

Data obtained after the administration of [illegible] A after [illegible] HR [illegible] (A) [illegible] HR [illegible] [illegible] recorded [illegible] [illegible] were obtained by [illegible]
HR Heart rate CI Cardiac index SI Stroke index BP Mean blood pressure SPT [illegible] TTI [illegible] TPR Total peripheral resistance MSER Mean systolic ejection rate LVSWI Left ventricular stroke work index

*Table 1—Cont'd*

| Patient Age (yr) | HR (per min) | CI (L/min/M²) | SI (ml/M²) | $\overline{BP}$ (mm Hg) | SET (sec/min) | TTI (mm Hg sec/min) | TPR (dynes sec cm⁻⁵ M²) | MSER (ml/sec/M²) | LVWI (Kg M/min/M²) |
|---|---|---|---|---|---|---|---|---|---|
| V M | 0 | 3 58 | 51 | 108 | 23 | 2 880 | 2 470 | 158 | 5 78 |
| 45 | 100 | 4 10 | 41 | 110 | 26 | 3 000 | 2 140 | 158 | 6 18 |
| | 170 | 4 10 | 34 | 108 | 30 | 3 350 | 2 110 | 136 | 6 05 |
| | 140 | 3 54 | 25 | 110 | 31 | 3 560 | 2 490 | 114 | 5 35 |
| | 110 A | 4 39 | 40 | 107 | 28 | 3 050 | 1 950 | 157 | 6 50 |
| | 120 A | 3 88 | 32 | 110 | 30 | 3 300 | 2 260 | 129 | 5 83 |
| | 140 A | 4 37 | 31 | 103 | 31 | 3 250 | 1 890 | 140 | 6 15 |
| | 160 A | 3 89 | 24 | 98 | 35 | 3 460 | 2 010 | 111 | 5 15 |
| W C | 87 | 3 44 | 42 | 101 | 25 | 2 670 | 2 370 | 137 | 4 74 |
| 37 | 100 | 3 79 | 38 | 100 | 26 | 2 700 | 110 | 145 | 5 17 |
| | 125 | 3 80 | 30 | 102 | 30 | 3 200 | 2 140 | 129 | 5 30 |
| | 137 | 3 82 | 28 | 104 | 32 | 3 380 | 2 180 | 118 | 5 30 |
| | 150 | 3 55 | 24 | 99 | 33 | 3 520 | 2 240 | 108 | 4 80 |
| | 130 A | 3 79 | 28 | 103 | 30 | 3 240 | 2 160 | 123 | 5 20 |
| | 133 A | 3 64 | 27 | 101 | 31 | 3 440 | 2 200 | 118 | 5 01 |
| | 148 A | 3 26 | 22 | 10[illegible] | 32 | 3 570 | 2 [illegible]50 | 10[illegible] | 4 7[illegible] |
| C L | 100 | 5 76 | 53 | 107 | 27 | 3 070 | 1 640 | 194 | 7 [illegible] |
| 44 | 110 | 5 28 | 48 | 107 | 29 | 3 180 | 1 640 | 180 | [illegible] 8[illegible] |
| | 130 | 4 72 | 36 | 107 | 3[illegible] | 3 060 | 1 830 | 149 | [illegible] 00 |
| | 150 | 5 78 | 35 | 98 | 34 | 3 400 | 1 500 | 157 | [illegible] 05 |
| | 134 A | 5 42 | 41 | 95 | 31 | 3 350 | 1 410 | 178 | 7 00 |
| | 138 A | 5 39 | 39 | 95 | 31 | 3 410 | 1 470 | 1[illegible]4 | 6 95 |

generally been made. In a study of the effect of atropine on coronary blood flow, Corlin[7] found that myocardial oxygen consumption per systolic second was unchanged by atropine, thus implying that the effect of atropine was solely related to its chronotropic property.

Atrial pacing provides a safe and effective means of producing increased heart rates. The impulses from the atrium are conducted through the A-V node and depolarize the ventricles in a normal fashion,[1] thus simulating sinus rhythm. Ross and associates[1] and Stern and co-workers have shown that alterations in heart rate within the physiologic range produce no change in the hemodynamic state. It is possible, therefore, to compare cardiac dynamics at similar heart rates obtained by atrial pacing and by atropine to determine whether atropine has any effects other than those related to its chronotropic property.

In the present study we found that the changes in cardiac dynamics produced by a dose of atropine sufficient to completely eliminate parasympathetic activity[1] were limited to those parameters which are directly influenced by changes in heart rate, i.e., SET, TTI, SI, and MSER. Those parameters which have been shown to be independent of heart rate, i.e., CI, LVWI, and TPR, remained unchanged. Braunwald and associates[1] have described the effect of sympathomimetic amines on shortening of the SET. Since the systolic ejection times at comparable heart rates before and after atropine are almost identical, one can infer that there is no unmasking of sympathetic activity and that therefore there is no parasympathetic tone acting to control this parameter under normal conditions. Atropine resulted in no change in TTI at comparable heart rates. *In so far as the TTI reflects myocardial oxygen consumption*, this confirms

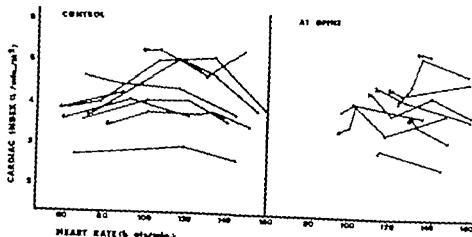



Fig 1 Comparison f cardia ndex t arious heart rate before and aft the intravenous administration of 2 mg of t pine ulf te

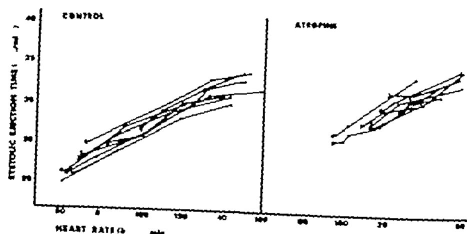



Fig 2 C mparison of s tol ject on time t ari us heart rat before nd after the intraven us administr t n f mg of atr pine ulfate

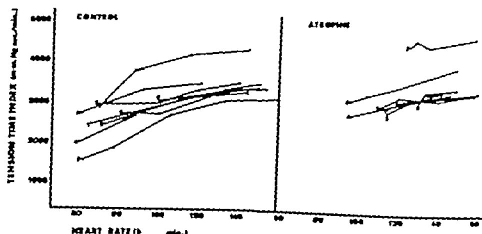



Fig 3 Comparison f the ten ion time ind x t various heart rates bef re an l after the tra en s ad ini tra tion of mg f atropine sulf te

Gorlin s findings The MSER has been used to describe left ventricular function because it is believed to reflect the velocity of muscle shortening[14] Its validity has been questioned under conditions in which the ventricular volume is changed[1] and therefore comparisons of MSER at different heart rates cannot be evaluated In this study the MSER was unchanged by atropine at similar heart rates and stroke volumes On the assumption that no significant change in ventricular volume occurred this implies that atropine has no effect on left ventricular function

In conclusion the major effect of parasympathetic blockade with atropine in normal human beings is an increase in heart rate Any alterations in the parameters that were studied can be accounted for on the basis of change in heart rate alone Although the effects of vagolytic intervention on atrial function have not yet been studied it is apparent that blockade of parasympathetic tone in normal subjects has no significant effect on cardiovascular hemodynamics

**Summary**

Cardiac outputs and arterial pressures were obtained in 9 normal subjects in whom various degrees of tachycardia were induced by atrial pacing before and after the intravenous administration of 2 mg of atropine At similar heart rates atropine produced no change in cardiac index stroke index brachial arterial pressure systolic ejection time tension time index total peripheral resistance mean systolic ejection rate or left ventricular work index It is apparent that the effects of atropine on cardiovascular hemodynamics are limited to those related to its chronotropic effect

We gratefully acknowledge the assistance of A Pedersen J Cumming I Carey M M rett J Hulbert and F D Cart

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# Superiorly oriented electrocardiographic axis in infants with the rubella syndrome

*Katherine H. Halloran, M.D.**
*Shyamal K. Sanyal, M.B.B.S.***
*Thomas H. Gardner, M.D.*
*New Haven, Conn.*

Left axis deviation or a rightward superiorly oriented mean electrical axis in the electrocardiogram is rare in infancy and, when present, is usually associated with specific cardiac anomalies such as the endocardial cushion defect. Since this electrical axis was observed in 12 of a series of 23 infants with congenital heart disease associated with the rubella syndrome, it is being reported as an unusual observation, with some speculation as to possible causes.

## Clinical data (Table I)

Following the rubella epidemic in the spring of 1964, 23 infants with congenital heart disease whose mothers had a history of rubella were observed at the Yale-New Haven Medical Center. Rubella virus was isolated from a throat swab culture in 21. Although multiple organ systems were involved, only the cardiac anomalies will be discussed. Cardiac catheterization was performed in 13 infants. A large left-to-right shunt (QP/QS > 2) through a patent ductus arteriosus was demonstrated in 9, 3 of whom had additional peripheral pulmonic stenosis. A left-to-right atrial shunt was observed in 4 of these infants, possibly through a dilated foramen ovale secondary to the large ductal shunt rather than representing a true atrial septal defect. A small to moderate-sized patent ductus (QP/QS < 2) was demonstrated in 4, 3 of whom had peripheral pulmonic stenosis. One of these also had a left-to-right atrial shunt, and another had probable pulmonic valvular stenosis.

The clinical diagnoses in those infants who were not catheterized are tabulated in Table I. Five are considered to have a patent ductus arteriosus, 4 a peripheral pulmonic stenosis, and 1 a tetralogy of Fallot.

Eight infants underwent surgery with division of the patent ductus.

## Electrocardiographic and vectorcardiographic data

*Method.* Twelve-lead electrocardiograms were obtained with a Sanborn Poly-Beam or direct-writing recorder, and vectorcardiograms were obtained with a Sanborn Poly-Beam recorder using the Frank

From the Department of Pediatrics, Yale University School of Medicine [illegible] New Haven, Conn.
This work was supported [illegible]
This paper was presented at the [illegible] Meeting [illegible]
[illegible]

Received for publication [illegible] 1966.

*Address: Department of Pediatrics, Yale University School of Medicine, 333 Cedar St., New Haven, Conn.
**Work done during the tenure of a Research Fellowship from the New Haven Heart Association [illegible]

*Table I. Clinical data*

| Axis | Case | Sex | Virus isolation | Catheterization | Surgery | Diagnosis |
|---|---|---|---|---|---|---|
| Superior | | | | | | |
| | 1 S D | M | + | + | + | PDA |
| | 2 L Z | M | + | + | + | PDA |
| | 3 R W | F | + | + | + | PDA |
| | 4 R Wo | F | + | + | + | PDA |
| | 5 J B | M | + | + | + | PDA, Peripheral PS |
| | 6 S C | F | + | + | – | PDA, Peripheral PS |
| | 7 W M | M | + | + | – | PDA |
| | 8 J A | M | + | + | – | PDA, Valve S, Peripheral PS |
| | 9 W A | M | + | + | + | PDA |
| | 10 E S | F | + | – | – | PDA |
| | 11 J M | M | + | – | – | PDA, Peripheral PS |
| | 12 M F | M | + | – | – | Peripheral PS |
| Normal | | | | | | |
| | 13 J G | F | + | + | + | PDA |
| | 14 D D | F | + | – | – | PDA |
| | 15 R S | F | + | + | + | PDA, Peripheral PS |
| | 16 J L | F | + | – | – | PDA |
| | 17 P M | F | – | – | – | Peripheral PS |
| | 18 J K | M | + | – | – | Peripheral PS |
| Right | | | | | | |
| | 19 S G | F | + | + | – | PDA, Peripheral PS |
| | 20 M A | F | + | – | – | PDA |
| | 21 C A | M | | – | – | Peripheral PS |
| | 22 A S | F | + | + | | PDA, Peripheral PS |
| | 23 A C | F | + | – | | Tetralogy |

PDA Patent ductus arteriosus; PS Pulmonic stenosis.

lead system. Records were obtained during the first 2 months of life in 16 infants, in 8 during the first week of life. Frontal vector rotation and direction were derived from simultaneously inscribed leads according to the method of Grant[1] when vectorcardiograms were not directly recorded. The mean electrical axis was estimated to the nearest 5 degrees and defined according to the criteria of the New York Heart Association. Interpretation of ventricular enlargement was based on the criteria of Keith and associates.[2]

*Results (Table II)*

RHYTHM. A normal sinus rhythm was present in all. One infant had premature ventricular contractions at the age 2 months; these did not persist. The Wolff-Parkinson-White syndrome, Type B, was observed in 1 infant at 3 weeks of age and has persisted to the present.

P WAVES. Tall peaked P waves were observed in Lead II in 4 infants with a patent ductus. One infant with a large ductus had electrocardiographic evidence of left atrial enlargement with a deeply negative P wave in Lead $V_1$.

P-R AND QRS INTERVALS. The duration of the P-R and QRS intervals were normal except in the case of the Wolff-Parkinson-White syndrome.

ELECTRICAL AXIS. A superior or leftward oriented mean electrical axis was observed in 12 infants ranging from −160 to 0 degrees. Before 2 months of age the majority were in the −90 to −180 degree quadrant (Fig. 1, A). After 2 months a shift in axis was noted in 7. In the axis shifted from the superior right quadrant to the left and in 2 it shifted to a normal or a right orientation (Fig. 1, B). In the infant without a superior orientation the axis was variable but none showed an extreme rightward deviation. In no case was there a shift from a normal to a superior axis. After division of the ductus the superior

*Table II. Electrocardiographic and vectorcardiographic data*

| Case | Age at time of ECG | Axis (degrees) | AE | VH | ST-T | Frontal vector: Rotation | Frontal vector: Maximum mean vector | Frontal vector: P or D | Comment |
|---|---|---|---|---|---|---|---|---|---|
| 1 S D | 1 mo | 140 | RAE | RVH | N | Fig 8 | Superior right | D | |
| | 3 m | 140 | RAE | RVH | N | Fig 8 | Superior right | P | |
| 2 [illegible] | 8 d | −135 | N | LVH | N | CC | Superior right | D | |
| | 6 m | 45 | N | N | N | CC | Superior left | I | Postoperative |
| 3 [illegible] | 1 d | 170 | N | N | N | CC | Superior right | D | |
| | 1 mo | + 90 | N | CVH | N | Fig 8 | Inferior right | I | |
| 4 R W | 2 mo | − 10 | N | CVH | N | | | | |
| | 4 mo | 45 | N | CVH | N | Fig 8 | Superior left | I | |
| 5 J B | mo | 0 | RAE | CVH | N | | | | |
| 6 S C | 6 d | 90 | RAE | CVH | N | C | Superior right | P | |
| | 6 mo | 60 | N | RVH | N | | | | |
| 7 W M | 1 mo | − 90 | LAE | CVH | N | C | Superior | I | |
| | 6 mo | − 40 | N | RVH | N | Fig 8 | Superior | I | |
| 8 J [illegible] | 4 mo | 160 | N | LVH | V | C | Superior right | P | |
| 9 W [illegible] | 16 da | 45 | N | WPW | N | CC | Superior left | I | WPW syndrome |
| 10 [illegible] S | 4 days | 150 | LAE | N | N | Fig 8 | Superior | D | |
| | 3 m | 0 | LAE | LVH | N | | | | |
| 11 J M | 3 days | −120 | N | N | N | Fig 8 | Superior right | D | |
| | 4 m | + 60 | N | CVH | N | Fig 8 | Inferior left | I | |
| 12 M [illegible] | 1 d | 150 | N | N | N | C | Superior right | D | |
| | 6 m | 0 | N | N | N | | | | |
| 13 J [illegible] | 4 m | + 60 | RAE | CVH | N | Fig 8 | Inferior left | I | |
| 14 D D | 5 mo | + 4 | N | CVH | N | | | | |
| 15 R [illegible] | ? mo | + 80 | N | CVH | N | | | | |
| 16 J [illegible] | ? mo | + 60 | N | LVH | N | | | | |
| 17 [illegible] M | 3 mo | + 60 | N | N | N | | | | |
| 18 J K | 5 days | + 90 | N | N | N | | | | |
| | 6 m | + 60 | N | N | N | | | | |
| 19 S C | 6 wk | +100 | N | RVH | N | Fig 8 | Inferior right | I | |
| 20 M [illegible] | 4 [illegible] | +115 | N | RVH | N | | | | |
| | 3 m | +100 | N | RVH | N | C | Inferior | I | |
| 21 C [illegible] | 5 m | +100 | N | N | N | C | Inferior | I | |
| 22 [illegible] S | 3 mo | +100 | N | N | N | | | | |
| 23 [illegible] C | 1 m | + 90 | N | RVH | N | | | | |

AE = Atrial enlargement; RAE = Right atrial enlargement; LAE = Left atrial enlargement; VH = Ventricular hypertrophy; RVH = Right ventricular hypertrophy; LVH = Left ventricular hypertrophy; CVH = Combined ventricular hypertrophy; WPW = Wolff-Parkinson-White; N = Normal; C = Clockwise; CC = Counterclockwise; P = [illegible]; D = [illegible]

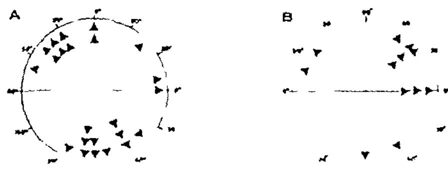



Fig. 1. A. The mean electrical axis [illegible] 2 months of age or less [illegible] B. The range of electrical axes after [illegible] months in the 17 infants who [illegible] (see text)

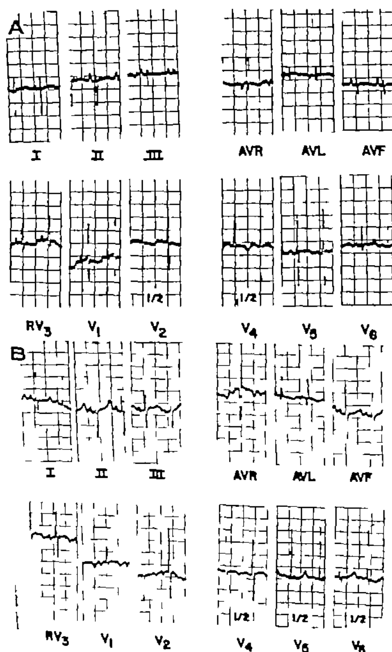



Fig. 2. Case 10, P.S. *A*, Age 4 days. Electrocardiogram shows an axis of −140 degrees and normal right ventricular preponderance in this newborn infant with a large patent ductus. *B*, Age 4 months. There is a shift in axis to 0 degree with evidence of left ventricular hypertrophy.

orientation persisted when it was present preoperatively.

VENTRICULAR HYPERTROPHY. In those infants with a superiorly oriented axis the precordial leads were indicative of right ventricular hypertrophy in 4, combined ventricular hypertrophy in 3, and appeared to be normal in 4 (Fig. 2). In those infants with a normal or a right axis there was right ventricular hypertrophy in 3, combined ventricular hypertrophy in 3, and left ventricular hypertrophy in 1, and 4 appeared to be normal.

VECTORCARDIOGRAMS. In those infants with a superiorly oriented axis the frontal vectors were variable. Rotation of the

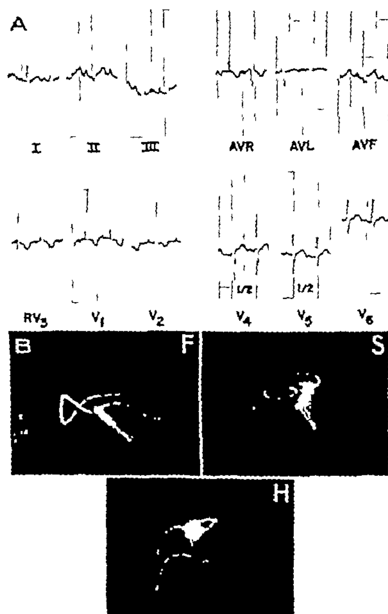



Fig. 3. C[illegible] W. M. [illegible] months. Infant with peripheral pulmonic [illegible] and [illegible] patent ductus. There [illegible] electrical axis of −40 degrees with [illegible] of right ventricular hypertrophy. B. The vectorcardiogram when the [illegible] 10 months [illegible] figure of eight predominantly counterclockwise superiorly oriented QRS loop in the frontal plane and anteriorly oriented predominantly clockwise QRS loop in the horizontal plane.

frontal vectors was clockwise in 3, counterclockwise in 3, and figure of eight in 5. After 3 months of age the rotation was counterclockwise or figure of eight in all but 1 (Fig. 3). The frontal vector showed one of four patterns (Fig. 4) and was oriented along the horizontal axis. There was a generally narrow loop even when the mean electrical axis in the electrocardiogram was calculated to be in the range of −90 degrees.

**Discussion**

The unusually high incidence of a superiorly oriented axis prompted a review of the data for possible correlation with cardiac diagnosis or ventricular hypertrophy. Although a clockwise extreme

FRONTAL VECTOR

Fig. 4. The four general patterns of the frontal QRS vectors generally oriented along the horizontal axis.

rightward vector orientation is present in approximately 3 to 5 per cent of normal newborn infants[4,8] in this group of infants it is found too frequently to be a normal variant. The shift from the superior right to the superior left quadrant could be related to the maturation of the pulmonary vascular bed and the normal progression from right-to-left ventricular dominance. The superior axis does not appear to correlate with right ventricular hypertrophy, however, since a shift from the superior right to the superior left quadrant occurred in cases of pure right ventricular hypertrophy. That it reflects left ventricular hypertrophy also seems to be unlikely because some patients with right ventricular hypertrophy had a left axis (Fig. 5) whereas in patients with left or combined ventricular hypertrophy the axis shifted to or was a right or normal axis. Furthermore, the distribution of hypertrophy was similar despite a shift in axis.

The frequency of left axis deviation occurring with a patent ductus is about 10 per cent in the literature.[6] In this series, however, a left or superior rightward orientation is present in 60 per cent. Since the majority has retained this axis during the first year of life, it is unlikely that a higher percentage would be uncovered in a series of patients with patent ductus if electrocardiograms were obtained as early in infancy. The distribution of diagnoses, furthermore, was similar in cases with and without a superior axis, the majority in each group having a patent ductus. The superior axis also did not shift toward normal when the ductus was divided.

The etiology of a left axis deviation or superior orientation has been a subject of interest in the literature. Recent investigations have demonstrated that left ventricular hypertrophy per se does not cause left axis deviation.[9] It has been suggested that when marked left axis

I II III AVR AVL AVF

RV3 V1 V2 V4 V5 V6

Fig. 5 [illegible]

deviation is present it is the result of a conduction disturbance in particular in the anterior division of the left main bundle branch[9] Myocardial fibrosis has frequently been implicated[10,11] Left axis deviation has been produced experimentally in the baboon heart by interruption of the anterior ramus of the left bundle branch[3] The well known association of left axis deviation with the endocardial cushion group of anomalies has been related to an anomaly of the left bundle branch system[3] A recent review correlating a dominant $S_1S_2S_3$ pattern in children with congenital heart disease included 2 cases of patent ductus arteriosus[1] but it was considered that this pattern usually signifies right ventricular hypertrophy In our series the 2 patients who retained an axis in this quadrant after the age of 2 months did have right ventricular hypertrophy

The extensive studies which were carried out after the rubella epidemic in 1964 have led to the concept of an active disseminated infection in affected infants involving multiple organ systems Virus can be cultured for some months after birth even in the presence of antibody in the newborn host and has been cultured from various organs at necropsy[1] The pathologic demonstration of myocardial necrosis and vacuolar degeneration in 2 infants with electrocardiographic evidence of severe myocardial damage suggests that active myocarditis may be present in some infants and it is conceivable that the conduction system could be affected[16] The general lack of correlation with ventricular hypertrophy or with the hemodynamic situation leads to the speculation therefore that this unusual superior orientation may reflect an abnormality of depolarization possibly directly related to the rubella syndrome which may be temporary or permanent

**Summary**

An unusual superiorly oriented mean electrical axis has been described in 12 of a series of 23 infants with congenital heart disease associated with the rubella syndrome The majority of infants had a patent ductus arteriosus or peripheral pulmonic stenosis The electrical axis did not correlate with the anatomic diagnosis or of ventricular hypertrophy and the possibility that this axis may represent a conduction disturbance is discussed

We wish to express our appreciation to Mrs Annette F[illegible] and Mrs Ann Marro for their technical assistance to Dr Norman S Talner for his review and criticism of the manuscript and to Dr Margaret Payne and Dr J F Barnevald for the [illegible] studies

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# Unusual features of pheochromocytoma

## An experience with 10 patients

N. O. Atuk, M.D.
J. L. Camp III, M.D.
J. J. Twomey, M.D.
A. B. Mesca, M.D.
Charlottesville, Va.

The correctability of the hypertension caused by pheochromocytomas makes their diagnosis and removal of the utmost importance. These tumors remain difficult at times to diagnose despite an ample literature on their clinical manifestations.[1-4] Their small size, inaccessible location, and frequently atypical clinical presentation contribute largely to this problem. This paper describes some atypical aspects of pheochrome tumors in an experience with 10 patients. The clinical features of these patients are summarized in Table I. The 24 hour urinary excretions of catechol amines, 3-hydroxy-4-methoxy mandelic acid (VMA), and 17-ketosteroids by some of these patients are listed in Table II.

### Methods

Urinary catecholamines were measured by the fluorometric method of von Euler and Floding.[7] No correction was made for recovery rate, which proved to be 72 to 85 per cent. Plasma levels of catechol amines were quantitated by the method of Aronow and Howard.[8] VMA excretion was measured by the method of Sunderman and co-workers,[9] and 17-ketosteroids by a modification[10] of the method described by Metcalf.[11] Total catecholamines were expressed as a percentage of their upper limits of normal, which was calculated as follows:

$$\text{Total catecholamines} = \left(\text{Norepinephrine (NE)} + \frac{\text{Epinephrine (E)}}{30} \times 100\right) \div 2$$

One hundred per cent is the upper limit of normal for total catecholamines by this expression. The reason for this is to give proportionate significance to both NE and E values, whose upper limits of normal excretion differ threefold. This is discussed elsewhere.[12]

### Case reports

*Case 1.* A 50-year-old white woman n t red in creasing nervousness, facial flushing, and menstrual irregularities during the year prior to admission. She also experienced heat intolerance, ex e e perspiration, and palpitation. She developed l ft ventricular failure shortly before admission. H per thyroidism was suspected but la ked ... but tau ... part fr m a basal metabol c rate of +60 per cent. Her serum protein bound ... 1 ne ... tr tion was 5.5 μg per cent.

She had ... sustained h pe ... ion ... 1 5 100 mm. Hg and a t ... h ... ardia f 130 per m ... te. She wa ... f ... erag build ... ppe ed i ... bo ... ntely ill. He f ... e w ... flushed ... The ex tremities were ... ld and p l ... She per p red p o fusely and was m ... b ... gently ... heart fa lure.

Her condition deteriorated rapidly, and she was no candidate for surgery when her catecholamine

From the Department of Internal Medicine, University of Virginia Hospital, Charlottesville, Va.
Received for publication ... 3 ... 26 1966.
Address for reprints: N. O. Atuk, M.D.

*Table I. Clinical features of 10 patients with proved pheochromocytomas*

| Patient | Age sex | Years with symptoms | Excessive sweating | Headache | Anxiety | Flush | Paroxysmal hypertension |
|---|---|---|---|---|---|---|---|
| 1 | 59 F | 1 | + | 0 | + | + | 0 |
| | 4 F | 2 | 0 | + | + | 0 | 0 |
| 3 | 35 F | 1 | + | — | + | + | + |
| 4 | 40 M | 15 | 0 | + | 0 | 0 | + |
| 5 | 57 M | ? | + | + | 0 | 0 | + |
| 6 | 4? F | 1 | + | + | + | 0 | + |
| | ?9 F | ? | + | + | 0 | 0 | 0 |
| 8 | 18 F | 3 | + | + | 0 | 0 | + |
| 9 | ?3 F | 1 mo | 0 | + | 0 | 0 | + |
| 10 | 58 F | 4 | + | + | 0 | + | + |

[illegible]

*Table II. Twenty four hour excretion of NE, E* and total catecholamines by 7 patients with proved pheochromocytomas and of 17 ketosteroids and VMA by some of these patients*

| Patient | NE (µg/24 hr) | E (µg/24 hr) | Total catecholamines (%) | VMA (mg/24 hr) | 17 Ketosteroids (mg/24 hr) |
|---|---|---|---|---|---|
| 1 | 5 6 | 180 | 493 2 | — | 1 4 |
| 2 | ( 0 | 431 | 1 086 6 | — | 25 8 |
| | 130 | 620 | 1 098 3 | | |
| 3 | ? (81 5 | 5 899 5 | 9 594 | — | 13 9 |
| | 1 1 9 5 | 4 951 5 | 11 173 2 | | |
| 4 | 1 240 | 9? | 7 4 5 | 15 | 13 9 |
| | 870 | 89 | 558 3 | | |
| 5 | 10 | 13 | 785 8 | 10 4 | — |
| | 4( | 1 | 318 | | |
| 6 | 480 | 151 9 | 558 | — | — |
| | 5(1 | 364 | 887 1 | — | — |

[illegible]

excretion was found to be increased. She required hemodialysis on her fourth hospital day because of renal failure and the retention of fluid. This lowered her plasma concentration of catecholamines significantly (Table III) and analysis of the bath fluid showed that this was at least partially due to the dialysis. The pallor of her skin cleared appreciably during the procedure. However, she failed to respond to repeated vomiting and died in pulmonary edema 2 days later.

At autopsy a solid benign pheochromocytoma weighing 80 gm was found in her left adrenal gland. She had bilateral pleural effusions, pulmonary congestion and hepatic venous congestion. There were small meningeal hemorrhages around the brain stem and in the substance of the mesencephalon. Renal failure was due to lower nephron nephrosis (Fig. 1). The arteries to the renal cortices showed moderate thickening and hyalinization and the glomerular capillaries were congested and had hemorrhaged into Bowman's spaces. There was also extensive central lobular necrosis in the liver

| Body build | Pharmacologic tests | Positive x-ray film | Location of tumor | Comment | Follow-up |
|---|---|---|---|---|---|
| Average | — | — | Left | Acute tubular necrosis; Congestive heart failure | Died |
| Obese | I | IVP [illegible] | Left | Neurofibromatosis | Normotensive |
| Thin | R | IVP; Tomo | Right | — | Normotensive |
| Obese | R | Tomo | Right | — | Normotensive |
| Thin | H | 0 | Right | Severe paroxysmal symptoms; Normal NE excretion | Normotensive |
| Obese | R | 0 | Bilateral | 20 pound gain in weight in preceding few years | Normotensive; Negative H test |
| Thin | H and R | IVP [illegible] | Right | Increasing intra-abdominal pressure caused attacks | Normotensive |
| Average | H and R | — | Right | Hyperventilation caused attacks. Malignant | Normotensive and well 9 yr. later |
| Thin | B | — | Left | Mild aortic insufficiency | Normotensive 10 yr. 30 pound gain in weight |
| Thin | — | — | Right | Stooping caused attack. Mild CVA | Normotensive 7 yr. later |

CVA, C[illegible] [illegible]

*Table III. The effect of hemodialysis on plasma levels of catecholamines and their concentration in the dialysis fluid after the procedure*

| | E (μg/L.) | NE (μg/L.) |
|---|---|---|
| A. Plasma | | |
| Before dialysis | 3.6 | 32.4 |
| After dialysis | 1.9 | 21.4 |
| B. Dialysis fluid (after hemodialysis) | 0.0 and 0.5† | 0.9 and 1.6† |

[illegible]
†[illegible]

Case 2. A 24 year-old white woman was known to have been mildly hypertensive for 2 years before she sought medical advice on April 14, 1959, [illegible] [illegible] throbbing frontal headaches and nervousness of recent onset.

On physical examination her pulse rate was 80 per minute and the blood pressure was 200/120 mm. Hg. She was obese, weighing 113 pounds, and had [illegible] [illegible] [illegible] position. Her skin was cold and [illegible] [illegible] [illegible] [illegible] [illegible] that she had [illegible] [illegible] [illegible] [illegible] [illegible]

[illegible] [illegible] [illegible] [illegible] [illegible] [illegible] bed [illegible] [illegible] [illegible] pressures of 40/40 mm. Hg during phentolamine test, a depressed left renal shadow, [illegible] the very [illegible] [illegible] suggestive [illegible] presence of a left supra[illegible] [illegible] presacral insufflation. [illegible] 24 hour excretion of urine contained 25.8 mg. of 17 ketosteroids.

The left suprarenal gland was [illegible] [illegible] [illegible] [illegible]. It contained a benign, solid, vascular, [illegible] [illegible] tumor that weighed 61 grams. Her blood pressure has averaged 130/85 mm. Hg [illegible] [illegible] [illegible] and she has been asymptomatic.

Case 8. A 18 year-old white [illegible] was hospitalized on Dec. 9, 1954, because of [illegible] [illegible] headaches [illegible] [illegible] [illegible] [illegible] [illegible] weakness. These symptoms were paroxysmal and had been present for about 1 year. Deep breathing [illegible] caused by exertion precipitated attacks.

Her pulse rate [illegible] ranged 90 per minute. During an attack her blood pressure rose to 80/150 mm. Hg from an average baseline of 120/80 mm. Hg. She was slightly agitated and was of average build. Her skin was moist but was of normal temperature.

Her blood pressure rose to 260/160 mm. Hg after 3 minutes of voluntary hyperventilation. This was

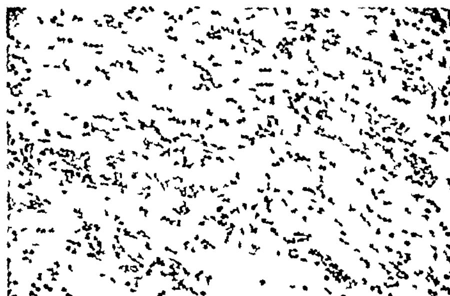


Fig. 2 C 1 Acute ren l tubular necrosis at autopsy There is destruction of tubular epithelium with flatten ing and some effort at regeneration by the remaining viable cells Many granular casts are evident

accompanied by the same symptoms which she had when be w dmitted f ve milligrams of phent lamine promptly lowered her blood pressure to 155/65 mm Hg with relief from her symptoms (Fig 7) A triangular shadow d torted the upper pole f h right kidney on an intravenous pyelo g m

At op ti wild pheochrome tumor weigh ing 1 5 g am w f un l in the right adrenal area It w rem d with great difficulty because it w adherent to the inferior en av the liver nd the d ph agm The tumor ppeared to be malig n nt on but logic examination Her convalescence wa unev ntful and he was asymptomatic and norm t n s 9 y ar later

## Comment

Pheochrome tumors are likely to be overlooked in patients whose symptoms and hypertension lack a paroxysmal pat tern Three of the patients whose clinical features are summarized in Table I main tained a persistent hypertension Their over all clinical pictures however did have many features to suggest the correct diagnosis It usually remains necessary to confirm these suspicions with pharmaco logic tests or catecholamine determinations

The presence of obesity is likely to bias the clinician In 1956 Kvale and asso ciates[13] commented We have yet to see an obese patient with a pheochromocy toma However obesity has been re ported in association with these tumors[1 4 5]

Clinical features suggestive of Cushing's syndrome were present in a few of these patients[1 4 14] Three of our subjects were overweight (Cases 2 4 6 Table I) but none of them appeared to have the Cushing syndrome However one patient excreted an excess of 17 ketosteroids (Case 2 Table II)

Increased adrenal cortical activity is not a feature of the usual nonobese patient with pheochromocytoma Yet adrenal cor tical hyperplasia[15 16] and adenoma[17] have been reported in association with these tumors In 3 other instances tumors of the adrenal cortex have functioned in the manner of a pheochromocytoma[18 4] An increased serum level of 17 hydroxycor ticosteroids has been described in a patient who had a functioning tumor of the organ of Zuckerkandl that increased further after massage of the tumor[21] Although the relationship between adrenocortical and medullary function remains obscure there is experimental evidence which sug gests that catecholamines accelerate 17 21 dehydroxycorticosteroid synthesis from progesterone in incubations of adrenal cortical homogenates[22] Perhaps the obesity and hypercorticism occasionally found in association with a pheochromocytoma are results of cortical stimulation by the prod

ucts of the medullary tumor. It is certainly not valid to exclude pheochromocytoma on the basis of obesity.

The acute tubular necrosis that occurred in Case 1 is a rare complication of pheochrome tumors. Carpenter and Kurvin[3] could find reference to only 3 other reports prior to their patient in 1961. Lower nephron nephrosis has also occurred in a patient who had an adrenal cortical adenoma and an increased rate of excretion of catecholamines.

The cause of the tubular lesions in pheochromocytoma remains uncertain. Oscillations of blood pressure to hypotensive levels, such as occurs during crises, may be a contributing factor, especially if renal blood flow has become impaired because of atherosclerotic arterial changes caused by prolonged exposure to hypertension. Postmortem studies performed in Case 1 suggest that ischemia due to arterial spasm played a major part in the necrosis of the renal tubules. Roentgenographic pictures were taken of the kidneys after arterial injection with 10 per cent vinyl plastic with bismuth oxychloride (Fig. 3 C). Her kidney showed marked cortical ischemia and arterial spasm when compared with a healthy control kidney

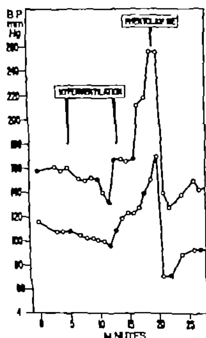



Fig. 2. Case 1. The effect of hyperventilation on the blood pressure and the prompt response to phentolamine.

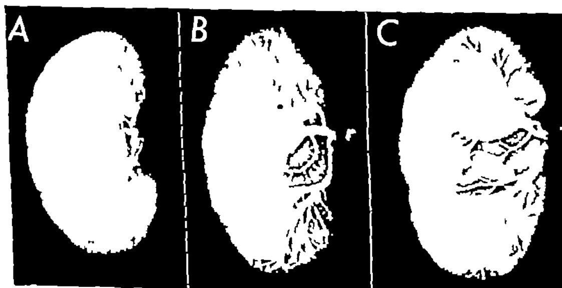



Fig. 3. Renal arteriograms from kidneys removed from (A) a healthy individual, (B) a patient with posthypotensive acute tubular necrosis, and (C) Case 1. Note the marked cortical ischemia and arterial spasm.

treated in the same fashion (Fig. 3A). This is not a feature of acute tubular necrosis as is evident from Fig. 3B. This patient died from acute tubular necrosis that resulted from prolonged shock. The histologic changes found in the arteries of the kidneys in Case 1 were not sufficient to account for the findings depicted in Fig. 3.

It would seem that this patient's kidneys were involved in a vicious circle. A high circulating level of catecholamines caused ischemic damage to her renal tubules. The renal failure that followed caused further retention of the noxious pressor amines. Hemodialysis proved to be partially effective in correcting this effect.

Case 2 had neurofibromatosis. The association of this neurocutaneous disorder and pheochromocytoma is well established. Over 40 instances in which these disorders coexisted have now been reported.[4, 18] Neurofibromatosis is readily diagnosed; when hypertension is present, it should alert the clinician to the possibility of a coexisting pheochromocytoma.

The danger of triggering an attack by manipulation of the tumor during operation is well known. Normal physical activities may also compress the tumor and express catecholamines into the circulation. Paroxysms were caused in our patients by the lifting of heavy objects, by lying in certain positions (Case 7), and by stooping forward (Case 10). A dramatic response to physical compression was illustrated in Case 5 (Fig. 2). The tumor was adherent to the patient's diaphragm, inferior vena cava, and liver. The movement of her diaphragm during hyperventilation compressed the tumor, which resulted in severe hypertension.

## Catecholamine dynamics in pheochromocytoma

The total 24 hour urinary output of catecholamines in 7 patients who had pheochromocytomas varied from 281 to 11,175 per cent of the upper limits of normal excretion (Table II). The day to day excretion did not fluctuate widely. There was no apparent relationship between which catecholamine predominated in the urine and the severity of the hypertension, nervousness, body build, metabolism, or levels of blood sugar.

The size that a pheochromic tumor attains before discovery depends on the symptomatology it generates. This is influenced by many factors. One element is the number of secreting tumor cells. Cystic tumors have relatively few functioning cells and reach a large size before they are discovered. Symptoms are also dependent on the rate at which the tumor releases catecholamines into the circulation. This is extremely variable, and recently it has been shown[4] that up to 90 per cent of the catecholamines produced by a pheochromic tumor may be ineffective because they are metabolized without being released into the circulation. Such ineffective catecholamine synthesis was observed in two malignant tumors.[19] This rapid degradation of catecholamines is reflected by an increased excretion of such metabolites as 3-hydroxy-4-methoxy mandelic acid (VMA), normetanephrine, and metanephrine. Only 0.3 to 4 per cent of the catecholamines infused intravenously may be recovered in the urine.[17] If this is analogous to the intravenous release of catecholamines from a pheochromic tumor, urinary catecholamine values will represent only 0.03 to 0.4 per cent of the amount made in tumors that have a high rate of degradation in situ.

There is also a wide individual variation in sensitivity to catecholamines. Most patients with pheochromocytomas are relatively insensitive to high circulating levels of the products of the tumor. Occasionally, hypertensive crises occur in patients while catecholamine excretion does not exceed normal limits.[5] Such patients show an unusual sensitivity to infused catecholamines when studied after removal of the tumor. Patients who have essential hypertension are also more sensitive to infusions of NE than are normotensive control subjects.[5]

Thus, the systemic effects of catecholamines and their excretion by a pheochrome tumor are governed by many factors. These include the amount of functioning chromaffin tissue present, the balance between release and degradation of catecholamines, and the sensitivity of the individual patient to their pharmacologic actions. It is evident from this complexity of factors that no chemical test can be used as a sine qua non to screen

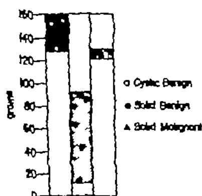



Fig. 4 The relative weight of the benign cystic and solid tumors and the malignant pheochromocytoma when removed

hypertensive patients for pheochromocytoma.

It is possible to speculate on the influence that these factors had on the size that the tumors attained in our patients before they were recognized. The cysts in some tumors contributed significantly to their weight without adding to their capacity for catecholamine synthesis. The observation that malignant pheochromocytomas actively degrade catecholamines in situ could explain why the malignant tumor in this series grew undetected to 125 grams. The solid benign tumors were significantly smaller (Fig. 4). The largest of these weighed 90 grams and was the only tumor that proved to be fatal. The smallest tumor weighed only 14 grams; the patient who had this tumor was quite symptomatic although urinary catecholamines and their metabolites were not greatly elevated (Table II, Case 5). An individual hypersensitivity to the pharmacologic action of catecholamines seems to have been likely in this patient. This tumor excreted only 10.8 mg. of VMA whereas a 44 gram solid tumor excreted 15 mg. of VMA in the urine over 24 hours. The larger benign tumors may have degraded catecholamines at a greater rate permitting themselves more time to enlarge before being diagnosed.

## Summary

The clinical experience with 10 patients who had proved pheochromocytomas is summarized. Some unusual features were encountered. These included lower nephron nephrosis, obesity, elevated urinary 17 ketosteroid excretion, neurofibromatosis and some unusual postural associations with clinical paroxysms. Catecholamine pathophysiology in pheochromocytoma was discussed.

We would like to thank Dr. J. Edwin Wood, Jr. for his encouragement in this study, Dr. K. R. Crispell for his valuable suggestions, Dr. A. D. Hart for his careful review of the manuscript, and Mrs. Suzanne Feller, Mrs. Roberta Wierzak and Mrs. Jo Ann Harris for their technical assistance.

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# Cardiac output in erythrodermic skin disease

*Gustav C Voigt M D **
*Herbert L Kronthal M D ***
*Robert G Crounse M D ****
*Baltimore Md*

Patients with extensive erythrodermic skin disease may present with dyspnea peripheral edema cardiomegaly hepatomegaly wide pulse pressure and elevated venous pressure[1,2] These findings have been interpreted by some investigators as indicative of high output cardiac failure[1,2] It is conceivable that the increase in circulation to the skin and subcutaneous tissues in extensive skin disease characterized by erythroderma would result in a significant increase in cardiac output Fox and associates[2] measured cardiac output in such patients and found high values in 2 patients who had psoriasis or exfoliative dermatitis The opportunity to observe a patient who had congestive heart failure with clinical signs of high cardiac output associated with a severe exacerbation of psoriasis prompted us to measure cardiac outputs in patients with erythrodermic skin disease This is a report of our findings in 6 patients

## Materials and methods

Six male patients with psoriasis or exfoliative dermatitis were studied The patients are described in Table I and in Fig 1 an illustrative case demonstrates the extent of disease present in these patients All of the psoriatics had at least 55 per cent of the skin area involved and those with exfoliative dermatitis had disease involving almost all of the body surface Three patients (J C E M and V M Table I) had congestive heart failure when first seen One patient E M had definite evidence of underlying heart disease Causes of high cardiac output such as fever anemia hyperthyroidism hypoxemia Paget s disease of bone arteriovenous fistula and beriberi heart disease were ruled out In most patients cardiac outputs were measured soon after acute exacerbations of chronic psoriasis or the onset of exfoliative dermatitis and usually before their skin disease was treated

The patients were not premedicated After the insertion of a venous catheter and an arterial needle the patient was allowed to rest for 15 minutes Cardiac output was measured using dye dilution by injecting indocyanine green into a peripheral vein and sampling from a brachial artery Car

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[illegible] supported in part by United [illegible] Public Health Service [illegible] No 2 R01 HF [illegible] [illegible] FR 35 [illegible] 1 F2 HE 25 [illegible]
Received for publication Feb 9 1966

*[illegible] Resident [illegible] Medicine [illegible] City Hosp[illegible] Baltimore Md [illegible] School of Medicine
**[illegible] Dermatology The Johns Hopkins University School of Medicine
***[illegible] Professor of Dermatology The Johns Hopkins University School of Medicine

*Table I. Summary of clinical findings and laboratory results in 6 patients with erythrodermic skin disease*

| Patient | Age (yr.) | Disease | Extent of disease (%) | Blood pressure (mm. Hg) | History and physical | Chest x-ray findings | ECG | C.I. (L./min./M.²) | S.I. (ml.) | H.R. (per min.) |
|---|---|---|---|---|---|---|---|---|---|---|
| J. B. | 33 | Psoriasis | 60 | 130/70 | — | Normal | Normal | 3.4 | 85 | 80 |
| J. C. | 39 | Exfoliative dermatitis | 90 | 140/80 | Dyspnea, cardiomegaly (?), 2+ edema | Normal | Normal | 3.8 | 95 | 82 |
| W. M. | 39 | Psoriasis | 55 | 110/70 | Hepatomegaly, 2+ edema | Normal | Normal | 6.0 | 99 | 96 |
| J. W. | 44 | Exfoliative dermatitis | 90 | 130/70 | — | Normal | Normal | 4.9 | 95 | 90 |
| E. M. | 62 | Psoriasis | 65 | 110/90 | Dyspnea, cardiomegaly, hepatomegaly, 1+ edema | Cardiomegaly | Atrial fibrillation, ST-T changes | 4.4 | 96 | 92 |
| A. M. | 73 | Exfoliative dermatitis | 85 | 150/80 | Dyspnea, cardiomegaly, hepatomegaly | Cardiomegaly | LVH | 5.5 | 103 | 95 |

[illegible]
[illegible] LVH, Left ventricular hypertrophy.

diac output was calculated by the pooled sample technique.[4] Duplicate determinations were made in each patient and the average of the two results is reported. The duplicate values varied from the average by ± 7 per cent or less.

## Results

The results are summarized in Table I and the cardiac outputs of our patients and the cardiac output in normal man are compared in Fig. 2. The normal values represent determinations of cardiac output in patients with normal hearts who have undergone cardiac catheterization in this institution and compare well with the results obtained in normal young men by other investigators.[3,5] Cardiac output was significantly elevated in 4 patients. Stroke volumes were also elevated but to a lesser degree, indicating that some of the increase in cardiac output was secondary to an increase in heart rate. Although none of the patients had tachycardia, their pulse rates were above normal resting values. This observation is similar to the findings in other diseases associated with high cardiac output.[10,11]

Two patients were studied again.

E. M., a 62-year-old man with arteriosclerotic heart disease and a long history of severe psoriasis, was restudied after 9 weeks of topical therapy with triamcinolone acetonide and occlusive plastic wrapping produced dramatic improvement in his skin disease. When he was first seen heart failure was present. About 65 per cent of his skin was involved by typical psoriatic plaques and marked erythema. His cardiac output was 9.1 liters per minute. After successful treatment of the psoriasis, scaling was minimal, erythema was absent, and much of the skin was smooth and pliable (Fig. 3). Without any changes in his diet

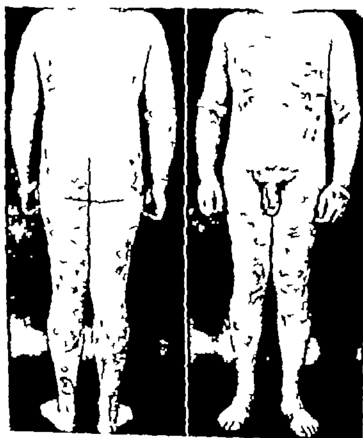


*Fig. 1. Photograph of J. B., age 33, illustrating the extent of disease. The patient had about 60 per cent of his body surface involved by psoriasis.*

activity or medications, the signs and symptoms of heart failure regressed. Cardiac output was measured again and had fallen to 5.0 liters per minute (Fig. 2). A concomitant increase in circulation time and decrease in venous pressure supported the clinical impression that heart failure associated with high cardiac output improved when the psoriasis responded to therapy (Table II).

W. M., a 59 year old man, had severe exacerbation of long-standing psoriasis when first studied. Typical psoriatic lesions associated with scaling and generalized erythema involved 57 per cent of his skin. Pitting pretibial edema and hepatomegaly were present, but it was not certain that he was in heart failure. Cardiac output was 9.5 liters per minute. Nine months later, after intensive treatment with intermittent systemic corticosteroids and methotrexate in addition to topical medications, he was much improved. Although the skin was still somewhat erythematous, there was no scaling and the skin was soft. Pretibial edema was not present. Cardiac output at this time was 5.1 liters per minute (Fig. 2). Circulation time increased, suggesting a decrease in the speed of circulation (Table II).

## Discussion

It has been estimated that the blood flow to the skin normally represents between 5 and 9 per cent of the total cardiac output. Although direct measurement of the blood flow to the skin is difficult, a few observations demonstrate that the cutaneous circulation is very flexible. Blood flow to the finger, which has a high surface area to volume ratio, has been shown to increase almost 100 fold with a change from a cold to a hot environment. In human adaptation to work in hot environments, a large

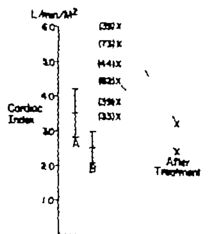



Fig. —A comparison of the cardiac output expressed by the cardiac index of patients with erythrodermic skin disease and normal man. The cardiac indexes of the patients are indicated by X and their ages are given in parentheses. A is the range of cardiac indexes in normal young men and B is the range of cardiac indexes in normal men over the age of 60. Two patients, 62 and 73 years old, have cardiac indexes which are more strikingly elevated when compared to those of normal men of the same age. Two patients 39 and 62 years old studied again after successful treatment of their skin disease demonstrated a decrease in cardiac index to normal values.

increase in circulation to the skin and subcutaneous tissue is brought about by an increase in blood volume and an elevation in cardiac output. The magnitude of these changes can be appreciated when the heart fails to maintain or to increase this output and serious hypotension occurs, as it does in some patients with heat exhaustion.[14,15] Studies of the capillaries in normal and diseased skin demonstrate significant increases in the size of these vessels in several pathologic conditions.

In diffuse skin disease characterized by erythroderma increased circulation to the skin can be appreciated clinically. It is conceivable that this increased circulation would result in an increase in cardiac output. The fact that cardiac output is elevated in some patients with erythrodermic skin disease supports this hypothesis. The cardiac outputs of 4 of our patients were elevated to the same order of magnitude as those reported in severe anemia, hyperthyroidism and Paget's disease of bone,[19-21] diseases in which high cardiac output has been documented and high

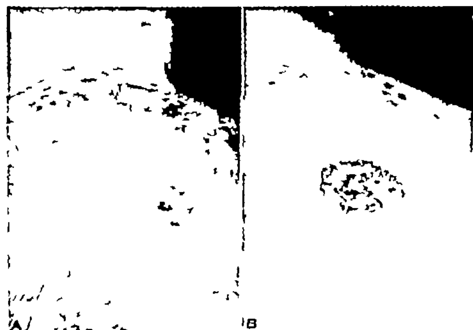



Fig. —Photograph of representative area of J. M., 62 year old psoriatic, before treatment. Cardiac output was 9.1 liters per minute. B. The same area after 9 weeks of therapy. There is an impressive decrease in scaling and erythema. Cardiac output had fallen to 5.0 liters per minute. The small psoriatic plaque in B developed just after successful therapy was provoked locally by curettage for an incidental lesion, an example of the Koebner phenomenon. No other such plaques were present.

*Table II. A comparison of hemodynamic findings in 2 patients before and after successful treatment of extensive psoriasis*

| Patient | Parameter | Before treatment | After treatment |
|---|---|---|---|
| E M | | | |
| | Circulation time (sec) | 32 0 | 20 0 |
| | Venous pressure (cm of saline) | 19 0 | 12 0 |
| | Cardiac output (L /min) | 9 1 | 5 0 |
| | Cardiac index (L /min /M ) | 4 4 | 2 4 |
| W M | | | |
| | Circulation time (sec ) | 11 0 | 13 5 |
| | Cardiac output (L /min ) | 9 5 | 5 1 |
| | Cardiac index (L /min /M ) | 6 0 | 3 2 |

[illegible]

output cardiac failure has been reported. Further evidence that cardiac output is elevated as a direct result of diffuse erythrodermic skin disease is obtained from the studies of 2 patients during exacerbations and remissions of severe psoriasis. Cardiac output decreased significantly, circulation time increased, and signs and symptoms of heart failure regressed when their skin disease responded to treatment.

Brandfonbrener, Landowne and Shock[1] have shown that there is a decrease in the cardiac output of normal man as age increases. They found a mean cardiac index of 2 45 liters per minute per square meter of body surface area in normal men over the age of 60 years. Two of our patients, ages 62 and 73, had cardiac outputs which were more strikingly elevated when they were compared to those of normal men of the same age (Fig. 2).

The fact that cardiac output is increased in some patients with erythrodermic skin disease appears to be clinically important. Several investigators reviewing large series of patients with exfoliative dermatitis and other erythrodermas point out that these diseases have a high mortality rate approaching 30 per cent in some series.[3,4] Edema, hepatomegaly, and tachycardia in the absence of fever are associated with these diseases and are often unexplained. The mode of death is not well understood but heart failure is occasionally described. It seems to be reasonable to conclude that high-output cardiac failure may be an important factor in the morbidity and mortality of erythrodermic skin disease, particularly in patients with underlying heart disease.


## Summary

Cardiac output was measured in 6 patients with erythrodermic skin disease. Four patients had a significant elevation of cardiac output. Satisfactory treatment of psoriasis in 2 patients resulted in a decrease in cardiac output and regression of heart failure. The significance of these observations is discussed.


We wish to acknowledge the assistance received from Dr. Louis Bernstein of Sydney, Australia, formerly Fellow in Medicine at this institution. We are indebted also to Dr. Richard S. Ross, Professor of Medicine, The Johns Hopkins University School of Medicine, for his invaluable guidance in the preparation of this paper.


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# An evaluation of the cardiac index

*Harold Smulyan, M.D.,**
*William A. Vincent, M.D.*
*Udomporn Kashemsant, M.D.*
*Richard P. Cudd, M.D.*
*Robert H. Eich, M.D.*
*Syracuse, N. Y.*

The body surface area taken from the Boothby and Sandiford nomogram as an estimate of body size is widely used to narrow the normal range of many physiologic measurements. One such measurement, the cardiac output, has a large scatter in normal subjects because of the variability inherent in the methods used and the physiologic variations in the subjects studied. It would seem that conversion of cardiac output to cardiac index would effectively reduce the scatter of normal cardiac output measurements by accounting for one of the covariables, body size. The cardiac index has been utilized in this way for many years, but its value has rarely been questioned. It is the purpose of this study to collect information in regard to the use of body surface area as a ratio standard for the cardiac output, to attempt to judge from this evidence whether such a practice is worth while, and, if it is found to be unsatisfactory, to attempt to develop a more useful method of correcting cardiac output for body size.

## Historical background

The first extensive work in the measurement of body surface area (BSA) was done by Meeh in 1879.[1] He made measurements in 6 adults and 10 children using various methods such as marking the body in geometrical patterns, winding strips of paper about the limbs, and cutting out and weighing pieces of paper which covered irregular portions of the body. He then devised a formula, the use of which produced results within 7 per cent of his actual measurements. This formula employed the two-thirds power of the weight since the surface area of two objects of the same shape are to each other as the two-thirds power of the volumes. Although several attempts were made to improve it, Meeh's formula was used for 37 years.

When the Russell Sage Institute of Pathology decided to express calorimeter results for the study of the basal metabolic rate in terms of BSA, they assigned the problem of measurement of BSA to an electrical engineer, Delafield DuBois. The results of his efforts were published in 1915. Five subjects were studied: (1) a 36-year-old cretin, short and stocky with a small head; (2) a 21-year-old subject, slightly stout; (3) a 21-year-old subject, tall, thin, and bony with little fat; (4) a 32-year-old subject, tall and of average

From the Department of Medicine, [illegible] New York Upstate Medical Center [illegible] Hospital, Syracuse, N. Y.
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[illegible] of New York Upstate Medical Center, [illegible] East Adams [illegible] Syracuse, N. Y. 13210.

build, and (7) a female, very short and very fat (no age given). These patients were dressed in tightly fitted underwear, thin socks, thin cotton gloves, and a section of the leg of a knitted undersuit pulled over the head and neck. Strips of manila paper were then pasted on until a flexible *but inelastic covering of the body was completed.* This covering was cut off with scissors and a mold of each section made by coating the inside with melted paraffin. The molds were then cut into small pieces and placed over sheets of weighed photographic paper, which were exposed, cut out, and weighed. *Hands were measured by making paraffin molds over cotton gloves* and other difficult areas, such as the genitalia, between the toes, behind the ears, etc., were traced separately. Usually only one arm and leg were measured. The method was thought to be accurate because repeat measurements of the bottom of a dish agreed within 0.1 per cent, two halves of one subject's body agreed within 0.5 per cent, and the measured surface of a bowling ball differed only by 0.13 per cent from the area calculated from the diameter.

The body was considered in regions—head, arms, hands, trunk (including neck), thighs, legs, and feet. For a given region various measurements of length and breadth were taken and their products related to the measured area of that region. A formula was then assigned which consisted of the product of the length, breadth (or girth), and a constant. Each was chosen to provide with the least variation the closest approximation to the measured area for the region. The BSAs were then predicted to be the sum of the calculated areas of all the regions. This was referred to as a method using the "linear formula."

In 1916 Sawyer, Stone, and DuBois[5] studied 7 more subjects in a similar fashion: (1) a 21 month old cadaver with rickets, small, pigeon breasted, who had died of pertussis; (2) an 18 year old male emaciated diabetic; (3) a 26 year old female sculptor's model; (4) a 21.5 year old male, tall and thin; (5) a 43 year old male who had lost both legs in a railroad accident (stumps atrophied, face fat); and (6) a 34 year old male who had lost both legs in an automobile accident. The seventh and later the third subjects were excluded because they had been covered with adhesive tape which it was suspected had stretched. This left 5 subjects whose measurements were used. Subject No. 5 had the head mold omitted, and Subject No. 6 had measurements of the trunk and thighs only. In Subject No. 2 an error was made *in the measurements for the location of the suprasternal notch.* This was discovered when the measured and calculated BSA did not check. Unfortunately, the patient had died and could not be remeasured. The authors therefore took measurements from several others of his build and used the average of these values in the formula for the area of the trunk.

In the same year[6] DuBois and DuBois discussed the difficulties in making the 19 measurements of length and girth necessary for the linear formula. They tested various other formulas using height and weight only, and selected constants which gave the least variation between measured and calculated areas. Their final formula was:

$$BSA = Weight^{0.425} \times Height^{0.725} \times 71.84$$

Use of this formula was associated with an average error of 1.5 per cent and a range of errors within ±5 per cent.

In 1921 Boothby and Sandiford[4] developed from the DuBois formula the nomogram used today, which relates height, weight, and body surface area. Berkson and Boothby[6] later affirmed the fact that the regression line of observed data for basal metabolic rate vs. BSA was very close to that of a ratio standard. In the scatter plot of one variable against another, a ratio standard line can be defined as one which is drawn through the origin of the graph and the intersection of the mean values for the two groups. These authors also tried to improve the relationship by using height and weight alone and several other exponents of height and weight. None of these approximated a ratio standard as well as the BSA calculated from the DuBois formula. This relationship suggested to Grollman[7] that BSA as calculated from height and weight was an indirect measure of the "active or metabolizing body size" and predicted the ratio of cardiac output (CO) to BSA to be reasonably constant. He studied 50 nor-

mal subjects under stringent basal conditions using the acetylene method for measuring CO and found this to be true. He suggested therefore that the cardiac output be corrected in this way and be called the "cardiac index."

Several other workers have also attempted to study this problem. Starr and associates,[9] using the ballistocardiogram; Taylor and Tiede,[10] using the ballistocardiogram and the acetylene method; and Brotmacher and Deuchar,[11] who did a search of the literature, all found low correlation coefficients between CO and BSA. Jegier and associates,[1] using an earoximeter on lightly anesthetized subjects, found a high correlation. Their subjects were children ranging in age from newborn infants to adolescents. The high "r" values found can be accounted for by the extremely wide range of body sizes studied, but the study does not resolve the problem in adults in whom the range of BSA is considerably smaller. Reeves and associates,[12] in studying 63 subjects free of cardiovascular disease, ages 5 to 45 years, thought that the relationship between BSA and CO was biologically obscure. These authors suggested that CO be related to A-V difference to account for differences in physiologic state, but this suggestion would not reduce the variability secondary to differences in body size. In summarizing this problem in his recent book, Guyton[13] stated that there was little basis for using BSA as a ratio standard in preference to weight or weight raised to a fractional power.

## Materials and methods

In order to investigate the relationship of CO to BSA under basal conditions, 72 male patients at a Veterans Administration Hospital were studied. These men were carefully selected for the absence of abnormalities or the administration of drugs known to influence the circulation, and were considered for purposes of this study to be normal. All subjects were acquainted with the procedures on the day prior to the study and were fasted after the evening meal. They remained in bed the following morning until 8 A.M., when they were brought to the laboratory by wheelchair. The patients were made comfortable in the supine position, and with the use of local anesthesia an 18 gauge Cournand needle was inserted into a brachial artery and a No. 18 intravenous needle was placed in the opposite arm. Thirty minutes of quiet rest was then interrupted only by measurement of auscultatory blood pressures and heart rates at 10-minute intervals. After this one-half hour of rest, oxygen consumption and $CO_2$ production was measured by collecting expired air in a 120 liter Collins gasometer. During this collection the cardiac output, repeat blood pressures, and heart rates were obtained. The patients then rested 10 more minutes, at the end of which time all measurements were repeated.

Concentrations of oxygen and $CO_2$ in the expired air were measured by the Scholander technique, and oxygen consumption, $CO_2$ production, and respiratory quotient were calculated in a standard manner. Cardiac output was determined by means of the indicator-dilution technique of Hamilton and Stewart, using radioiodinated ($I^{131}$) human serum albumin as the indicator and a timed 2 second interrupted arterial sampling technique.[1] At the conclusion of the study, the height and weight were measured on a standard hospital scale, and the BSA was determined from the Boothby and Sandiford nomogram.[3]

In order to insure that these patients were stable, subjects were only included in this group when their first and second measurements were reproducible, that is, there was (1) less than 10 mm. Hg variation in systolic blood pressure, (2) less than 4 beats per minute variation in heart rate, (3) less than 0.15 variation in measured respiratory quotient, and all respiratory quotients were less than 1.0, and (4) less than a 15 per cent variation in oxygen consumption. The CO values of all subjects who met the above-mentioned criteria were used, and all others were rejected for this analysis.

The data on height, weight, BSA, and CO from a second group of 60 normal subjects selected from the hospital population in the same way were taken from measurements made preliminary to other investigations carried out in this laboratory in the last few years. Although these also

*Table I. Mean and reproducibility of basal values. N = 22*

| | Age (yr.) | Height (cm.) | Weight (Kg.) | BSA (M²) | BP (mm. Hg) I S | BP (mm. Hg) I D | BP (mm. Hg) II S | BP (mm. Hg) II D |
|---|---|---|---|---|---|---|---|---|
| Mean | 39 | 175 | 71.4 | 1.86 | 119 | 71 | 117 | 73 |
| S.D. | 7 | 7.6 | 15 | 0.21 | 12 | 9 | 11 | 8 |
| Mean—Difference | | — | — | — | — | — | 2.7 | .7 |
| S.D. of difference | — | — | — | — | — | — | 2.6 | 3.5 |
| Coefficient of variation of difference† (%) | — | — | — | — | — | | 2.2 | 4.9 |

[illegible]
†Coefficient of variation of difference = S.D. of difference [illegible] × 100 [illegible]

were normal subjects, no attempt was made to insure a basal state as in the previous group. The data from this nonbasal group was used for comparison with the data from the basal group.

In addition to the values from the 82 normal subjects, information in regard to CO and BSA was taken from a detailed search of the literature on 324 normal subjects,[16-41] making a total of 406 pairs of data. When available, age, weight, and height were also recorded. In these references, when both Fick and indicator dilution measurements of CO were made in the same subjects, the indicator dilution COs were taken; when only the Fick method COs were recorded, these were used; when duplicate determinations of CO were noted, only the first of the pair was used. These data were divided into two groups—basal and nonbasal. When the information in the references indicated that the subjects were studied fasting, without sedation, shortly after arising, and with an attempt to allow quiet rest prior to the measurement, the values were assigned to the basal group. Other data were assigned to the nonbasal group. We appreciate the fact that patients assigned to the basal group from different studies may vary in the degree to which a true basal state was attained. The information thus obtained was punched into IBM data processing cards, and standard statistical analyses were calculated on a 1620 IBM computer.

## Results

The data which characterize the 22 subjects studied under controlled conditions in this laboratory are set out in Table I. The reproducibility of the blood pressure, oxygen consumption, heart rate, and R.Q. is excellent because of the exclusion of subjects who were not steady with regard to these variables. With the steady and presumably near basal states defined in this way, it is important to note that the CO values, which were not included in the definition for inclusion in this group, were also highly reproducible. The variability in CO measurement of approximately 4 per cent is probably close to the experimental error inherent in the method. Although it would appear to be difficult to attain a true basal condition in any subject whose brachial artery and antecubital vein have been cannulated, this group seems to be close to that goal.

The measurements made in this series of patients were related to each other with the use of the correlation coefficient. The data are shown in Table II under the heading of Basal. This group provided a range of BSAs from 1.58 to 2.48 M² and of COs from 3.1 to 10.0 L./min. The correlation coefficient for CO vs. BSA under these basal conditions was +0.43

| CO (L/min) | | Heart rate per min | | Vo ( c/m n) | | R Q | |
|---|---|---|---|---|---|---|---|
| I | II | I | II | I | II | I | II |
| 7 33 | 7 19 | 76 | 5 | 732 | 241 | 0 86 | 0 86 |
| 1 47 | 1 38 | 11 | 12 | 33 | 45 | 0 0 | 0 06 |
| — | 0 32 | — | 1 5 | — | 14 3 | — | 0 05 |
| — | 0 31 | — | 2 0 | — | 11 1 | — | 0 04 |
| — | 4 | — | 6 | — | 4 8 | | 4 |

*Table II Correlation coefficients—Syracuse data*

| Relationship | | Basal | | | Nonbasal | | |
|---|---|---|---|---|---|---|---|
| | | | p value | | | p value | N |
| CO | BSA | 0 43 | <0 05 | | 0 38 | <0 005 | 60 |
| CO v | weight | 0 43 | <0 05 | | 0 01 | <0 9 | 60 |
| CO v | height | 0 29 | <0 70 | 2 | 0 14 | <0 3 | 60 |
| CO s | Vo | 0 4 | <0 001 | 44 | — | — | — |
| V v | BSA | 0 57 | <0 00 | 2 | — | — | — |
| V | weight | 0 61 | <0 003 | 22 | — | — | — |
| V | height | 0 31 | 1 5 | 27 | — | — | — |
| V | card ac index | 0 51 | <0 005 | 44 | — | — | — |

*Table III Correlation coefficients—Literature data*

| Relation h p | | Basal g oup | | | Nonbasal group | | | All p in | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | p | N | | p | N | | p | N |
| CO | BSA | 0 | <0 001 | 167 | 0 3 | <0 001 | 39 | 0 34 | <0 001 | [illegible] |
| CO v | w ght | 0 34 | <0 01 | 60 | 0 41 | <0 001 | 150 | 0 39 | <0 001 | 210 |
| CO | height | 0 5 | <0 5 | | 0 43 | <0 001 | 134 | 0 40 | <0 001 | 161 |
| CO | age | −0 0 | <0 40 | 131 | −0 | <0 001 | 171 | −0 70 | <0 001 | 30 |
| CO | ight | 0 34 | <0 01 | 60 | 0 40 | <0 001 | 150 | 0 39 | <0 001 | 210 |
| CO v | height | 0 5 | <0 | | 0 45 | <0 001 | 134 | 0 40 | <0 001 | 161 |
| CO v | he ght/we ght | −0 48 | <0 01 | | 0 3 | <0 001 | 133 | 0 34 | <0 001 | 158 |
| CO | I ght and wei ht | — | — | — | — | | — | 0 44 | <0 001 | 160 |

at the lower limit of statistical significance ($p < 0.05$). It is of interest that body weight alone when compared to CO had an equally good correlation coefficient. The excellent coefficients of correlation found between CO and oxygen consumption and between oxygen consumption and BSA are well known. Again, body weight had a correlation coefficient not significantly different ($p < 0.50$) from that of BSA when both were related to oxygen consumption ($r = +0.61$ and $+0.57$, respectively).

A plot of CO vs BSA in this basal group is shown in Fig. 1. This can be compared to a similar graph of the data taken from 60 normal patients when no attempt was made to assure a basal state (Fig. 2).

From these figures and from the data given in Table II, it can be seen that the relationship between CO and BSA is similar in the basal and nonbasal states ($p < 0.50$). The standard error of estimate for both basal and nonbasal regressions in Table II varied from 1.34 to 1.56 L/min.

A similar analysis of all of the foregoing data plus the data taken from the search of the literature is presented in Table III. It is obvious that both the "basal" state and methodology of measurement of CO varied from laboratory to laboratory, and these factors probably largely account for the lower "r" values found in all categories when comparison is made with the basal group from this laboratory (shown in Table II). In order to study further this

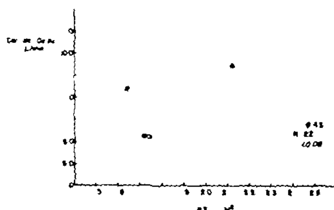



Fig. 1. Scatterplot of cardiac output vs. body surface area in 2[illegible] normal subjects under basal conditions.

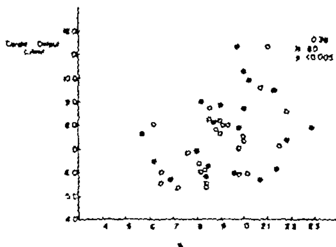



Fig. [illegible] 60 [illegible]

over all scatter the data from each laboratory contributing to the 406 pairs of CO and BSA were analyzed using a chi square test for homogeneity This test ($p < 0.50$) documented the homogeneity of the data and permitted the consideration of all of *the data as a single group*

The literature values analysis of which is shown in Table III always included at least the CO and BSA When height weight and ages were given this information was also recorded The number of these values are therefore *smaller than* that of the BSA group It is evident from Table III that the level of statistical significance found for the various correlations depends more on the size of the group than on the differences in the r values themselves The correlation coefficients for CO vs BSA in the basal and nonbasal groups were not significantly different ($p < 0.20$) which suggests that division of the data into basal and nonbasal groups adds little information not found in the analysis of the entire group For the entire 406 pairs the correlation coefficient for CO and BSA was +0 34 but the correlation coefficients for CO vs weight and height were +0 39 and +0 40 respectively Attempts to improve these coefficients by correlating CO with height and weight raised to fractional powers were unsuccessful Similarly unsuccessful was the attempt to correlate CO to the height weight ratio used as an estimate of stature The best correlation ($r = +0.44$) was obtained when CO was related to height and weight in a multiple regression analysis The standard error of estimate for all of the regressions in Table III ranged from 1 43 to 1 58 L min

The negative correlation of CO vs age ($r = -0.30$) has been previously shown[4] and is again demonstrated here

**Discussion**

The measurement of body surface area by DuBois in 1915 was a singular technical achievement But when consideration is given to the fact that the entire measured group numbered only 10 patients in several of whom the measurements were incomplete the confidence placed in this measurement by many years of routine use seems to be unjustified Some of this early confidence arose from the observations that the regression line of the plot of large numbers of measured basal metabolic rates against BSA very nearly intercepted the origin of the graph and closely approximated the slope of the line which represented BSA as a ratio standard[4] Whether this relationship is fortuitous or has real physiologic meaning is unclear In either case similar justification for use of the BSA as a ratio standard for the CO is not available

In 1949 Tanner[49] published a lucid description of the problems and assumptions made when a ratio standard is used He pointed out that when any data is reported as an index such as CO BSA there is an implied proportionality between the two parameters such that the regression line relating them is straight intersects the ordinate or abscissa at or near the origin and has a slope similar to the ratio standard line The greater the difference between the regression line of actual measurements and the ratio standard line the poorer that ratio standard will be This is so because normal values at increasing distances from the means will be considered to be more and more abnormal when expressed as an index This point is illustrated in Fig 3 where the regression line representing all 406 measured values of CO and BSA is plotted on the same graph as the ratio standard It can be seen that the regression line does not go through the origin In addition the slope of the regression line is such that large normal subjects would be suspected of having abnormally low COs if normality were predicted on the basis of the ratio standard The converse would be true of small individuals Fig 4 is a similar plot of CO vs weight which illustrates the same difficulty Fig 5 shows the opposite problem when the regression and ratio standard lines are plotted for CO vs height

It can be shown statistically as described by Tanner[49] that of the three the BSA ratio standard line is closest to its actual regression line This method states that when the ratio of the coefficients of variation (CV) of the independent and dependent variables is equal to the correlation coefficient which relates them the regression and ratio standard lines are

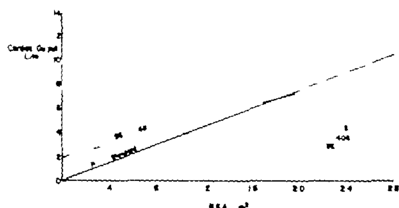


Fig. 3 Comparison of the regression line of the literature ... for cardiac output on body surface area and th... two standard line for the same group

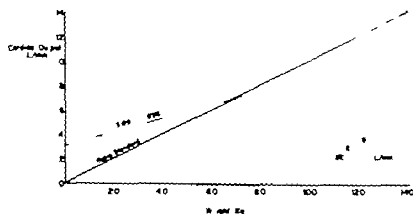


Fig. 4 Comparison of the regression line of the literature values for ... rdiac output on body weight and the ... standard line for the same group

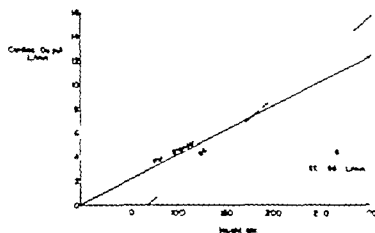


Fig. 5 Comparison of the regression line of the literature values for cardiac output on height and the ... standard line for the same group

identical. Conversely, the greater the discrepancy between CI : CI's and the r value, the poorer the ratio standard will be. In the present study, for the overall literature review:

$$\frac{CI : BSA}{CI : CO} = 0.47 \qquad r = +0.34$$

$$\frac{CI : Height}{CI : CO} = 0.734 \qquad r = +0.40$$

$$\frac{CI : Weight}{CI : CO} = 0.712 \qquad r = +0.40$$

The discrepancy between CI ratios and r is least when BSA is used and of the three it should therefore be the best ratio standard. Height and weight have higher correlation coefficients with CO but would clearly be poorer ratio standards because of the larger differences between their regression and ratio standard lines. At a 0.05 confidence level, however, all three regression lines differed from their respective ratio standard lines. These difficulties could be circumvented by using the regression formula for weight, for example, to predict the normal CO rather than using any ratio standard. Such a prediction would carry a standard error of 1.5 L./min. Since the use of multiple regression of height and weight on CO offers a somewhat higher correlation coefficient, and since height and weight are already routinely recorded in most laboratories, it would seem to be most reasonable to use the multiple regression formula for the purpose of predicting normal CO from body size. This formula, calculated from the 160 values where these data were available, is:

CO (L./min.) = [illegible] + 0.033 × weight (kg.) + 0.039 × height (cm.) with a standard error of 1.46 L./min.

Using this method, a predicted CO on the basis of height and weight could be calculated. If the observed CO fell within ±1.5 L./min. of the predicted value, the observed CO would be within one standard deviation of a group of known normal individuals with similar heights and weights. Judgments in regard to normality could be made on this basis.

It is unfortunate that of the 406 CO's reviewed in only 160 instances was height and weight also recorded. Nonetheless, this does represent a fairly large normal group with which others may be compared.

Ideally, the technique of multiple regression could be extended to larger groups of normal subjects and include in addition to height and weight other determinants of the resting CO, such as age, sex, heart rate, and oxygen consumption. This analysis could then account for more of the variability seen, but might become unwieldy for practical use. In any case, the method described based on available data would seem to be a better method for assessing the normality of the CO than the use of the DuBois BSA as a ratio standard.

## Summary

The value of using the body surface area to correct cardiac output for body size (cardiac index) has been studied in several ways. Its historical development has been traced and an attempt made to point out the strengths and weaknesses of the early data. Cardiac output and body surface area were correlated from 72 normal basal subjects and 60 normal nonbasal subjects from this laboratory. These results demonstrated a significant correlation of these variables in the basal and nonbasal states. It was also found in these subjects that when basal the cardiac output correlated equally well with body weight. Because the groups were small, 324 normal cardiac outputs and body surface areas were taken from the literature and added to the previous groups, totaling 406 such pairs for analysis. These results showed that the correlations of cardiac output with height and with weight were slightly better than that with body surface area. The importance of discrepancies between regression and ratio standard lines was discussed, and it was found that although the body surface area was the best ratio standard for cardiac output of the variables studied, it had a lower correlation coefficient and differed significantly from a regression line of normal values. It is suggested that the best solution is the avoidance of the use of any ratio standard, but rather the prediction of the normal cardiac output from height and weight on the basis of a multiple regression an-

dyals from a large group of normal subjects. Such a regression formula is presented.

We wish to thank Dr. Robert Gilbert and Dr. Richard Oite for their assistance with the statistical analysis. Data was processed in the Research Computer Center of the Upstate Medical Center.

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# Experimental and laboratory reports

## Incidence of ectopic beats as a function of basic rate in the ventricle

*Jiok Han, M.D., Ph.D.*
*John DeTraglia, B.S.**
*David Millet**
*Gordon K. Moe, M.D., Ph.D.*
*Utica, N.Y.*

A number of clinical observations have shown that early ectopic beats occur in the ventricle more frequently when the basic frequency is relatively slow. For example, Langendorf and associates[1] reported that early ectopic beats develop more frequently after relatively long cycles in the ventricle in patients with atrial fibrillation. Zoll and Linenthal[2] and their co-workers observed that premature ectopic beats occur more frequently in the ventricle when the basic idioventricular rate is relatively slow in patients with complete A-V block, and the incidence of ventricular fibrillation is also higher at slower frequencies in these patients. When the ventricular rate was increased by electrical stimulation or by infusion of catecholamines,[3] the frequency of occurrence of premature beats decreased. Han and colleagues[4] have recently suggested that the observed increase in the incidence of premature ectopic beats and fibrillation at slow ventricular frequencies might result from an increase in the degree of asynchrony of recovery of excitability in the ventricle at slow ventricular rates. Their experiments on dog ventricles have shown that the range of refractory period is greater and the fibrillation threshold is lower in the ventricle at lower basic frequencies than at higher rates. The possible role of asynchrony of recovery of excitability in facilitating re-entrant ectopic activity has been emphasized repeatedly in previous papers.[4,5]

To test the effect of basic rate on the incidence of early ectopic beats in the ventricle, the present experiments were performed on dog ventricles under some of the conditions which are known to facilitate the induction of ectopic activity and fibrillation in the ventricle.

### Methods

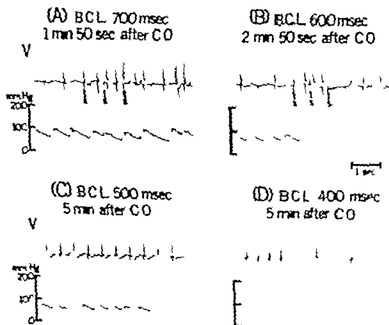
Experiments were performed on mongrel dogs which weighed 10 to 20 kilograms and were anesthetized by intravenous injection of sodium pentobarbital in a dose of 3[illegible] mg per kilogram. Under artificial respiration the chest was opened in the midline and the heart was cradled in the opened pericardium. To permit observations at slow frequencies, the S-A node was inactivated by crushing. When a further reduction in the heart rate was necessary, the right or left vagus nerve was stimulated below a crushed area. Stimuli were square pulses of 2 msec. duration at a frequency of 10 per second applied at a voltage sufficient to reduce

From the [illegible] Medical [illegible], Utica, N.Y.
This work was supported by [illegible] New York [illegible]
Received for publication Dec. [illegible]
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the heart rate to about one cycle per second. Stimuli were sometimes applied to the vagus nerve at a voltage sufficient to produce complete A-V dissociation.

The bipolar stimulating and recording electrodes were usually attached to the anterior surface of the left ventricle. Sites of stimulation and recording were separated by about 6 mm. A waveform generator was used to trigger a Tektronix pulse generator which delivered rectangular pulses of variable frequency, duration, and intensity through an isolation transformer to the bipolar stimulating electrodes. At each basic cycle length the ventricle was driven by 2 msec pulses at two times the threshold voltage. When the ventricle was driven by paired electrical stimuli, the waveform generator triggered two Tektronix pulse generators which in turn delivered paired pulses ($S_1$ and $S_2$) of 2 msec duration to the same pair of stimulating electrodes through the same isolation transformer. At each basic cycle length ($S_1S_1$), the interval between paired stimuli ($S_1S_2$) could be varied by changing the delay between the pulse generators. Electrical responses of the ventricle were recorded on a Grass polygraph at a speed of 75 mm per second. The aortic pressure was recorded by means of a Statham pressure transducer attached to a cannula in the aortic arch.

In experiments in which the effect of coronary occlusion was studied, the anterior descending branch of the left coronary artery was dissected free for a few millimeters near its origin in order to permit application of a clamp. Abrupt increases in aortic pressure were produced in some experiments by applying a clamp to the descending aorta just below the arch. In some experiments hypothermia was induced. After heparinization the blood from a femoral artery was passed through a coil immersed in an ice bath and returned to the dog through the femoral vein on the same side. The temperature of the blood in the heart was measured by a thermocouple introduced into the right atrium through the right external jugular vein.




[illegible] ectopic beats [illegible] found [illegible] the [illegible] left coronary artery (CO) at different basic cycle length (BCL). The upper traces [illegible] ular responses [illegible] the lower traces show the aortic pressure [illegible]

## Results

*Coronary occlusion.* For this group of experiments, the stimulating and recording electrodes were attached to the anterior septal margin of the right ventricle on the edge of the area where ischemia extends during occlusion of the anterior descending artery. While the ventricle was driven at basic cycle lengths between 400 and 800 msec, the anterior descending branch was clamped. If ectopic beats occurred, the clamp was removed immediately. If no ectopic beats occurred, the clamp was released after 5 minutes of occlusion. Repeat occlusion trials began about 20 minutes after the previous release of the clamp. The results of a representative experiment are illustrated in Fig. 1. In *A*, the artery was occluded while the ventricle was driven at a basic cycle length of 700 msec; several ectopic beats occurred 1 minute and 50 seconds after the start of occlusion. In *B*, the ectopic beats occurred 2 minutes and 50 seconds after the start of occlusion when the basic cycle length was 600 msec. No ectopic beats occurred during 5 minutes of occlusion at basic cycle lengths of 500 msec in *C* and of 400 msec in *D*.

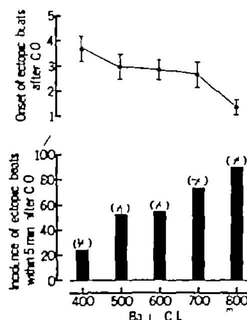



Fig. 2 Th[illegible] ... [illegible] in the upper part for different [illegible]

Similar results were consistently observed on repeated trials of coronary occlusion in 8 dogs; the cumulative data are shown in Fig. 2. Ectopic beats occurred within 5 minutes after the start of occlusion in 10 of 11 trials (91 per cent) at a basic cycle length of 800 msec, with an average time of onset of 1 minute and 24 seconds. Ectopic beats developed 2 minutes and 40 seconds after the start of occlusion in 12 of 16 trials (75 per cent) at a basic cycle length of 700 msec, 2 minutes and 55 seconds in 9 of 16 trials (56 per cent) at 600 msec, 2 minutes and 58 seconds in 9 of 17 trials (53 per cent) at 500 msec, and 3 minutes and 44 seconds in 4 of 17 trials (24 per cent) at 400 msec. Analysis of variance indicates that the average time of onset of ectopic beats is a significant function of the basic cycle length at the level of $p < 0.05$.

*Abrupt increase in aortic pressure.* The effect of abrupt increase in the aortic pressure was studied in 4 dogs, and the results of one of these experiments are shown in Fig. 3. While the ventricle was driven at various basic cycle lengths between 400 and 800 msec, the descending aorta was clamped for 10 seconds and the incidence of ectopic beats was recorded. Repeat trials of aortic occlusion began about 5 minutes after the previous release. While the ventricle was driven at a basic cycle length of 800 msec in *A*, the clamp was applied at the time indicated by an arrow. An early ectopic beat occurred about 3 second after the clamping when the aortic systolic pressure had increased to 195 mm Hg from the control of 100 mm Hg. A premature beat occurred about 3 second after the clamping when the aortic pressure increased to 200 mm Hg from 110 mm Hg at a cycle length of 700 msec in *B*. No ectopic beats occurred at cycle lengths of 600, 500 and 400 msec in *C*, *D* and *E*, respectively, during 10 second of a comparable increase in aortic pressure.

Similar results were observed in all 4 dogs; the cumulative results are illustrated in Fig. 4. Ectopic beats occurred in 13 of 14 trials (93 per cent) at a basic cycle of 800 msec, and with progressively decrea

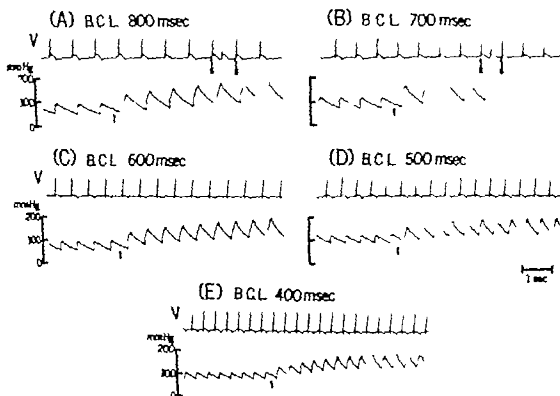



Fig. 3. Exp. 5-17-65. Premature ectopic beats induced in the ventricle by a sudden increase in the aortic pressure at different basic cycle lengths. The upper traces show ventricular responses and the lower traces show the aortic pressure. In the lower traces the time of the clamping of the descending aorta is indicated by an arrow.

ing frequency at higher driving frequencies. As shown in the upper part of the figure, the average elevation of aortic pressure was quite similar at all basic cycle lengths.

*Hypothermia.* In the experiment depicted in Fig. 5, ectopic beats developed in the spontaneously beating ventricle when the temperature of the blood in the heart was decreased to 24-26 C. The ventricle was then driven by basic stimuli for 30 seconds at each of several basic cycle lengths between 600 and 1,200 msec, while the occurrence of ectopic beats was observed. Ectopic beats developed at basic cycle lengths of 1,200 and 1,000 msec in A and B but not at 800 and 600 msec in C and D. Repeat observations were made many times in 3 dogs and the cumulative data are shown in Fig. 6. The incidence of ectopic beats decreased progressively as the driving frequency was increased. No ectopic activity occurred at basic cycle lengths of 700 and 600 msec.

*Paired pulse stimulation.* The technique of paired pulse stimulation has been used to slow the effective rate and to augment the force of contraction in the ventricle. Since the second pulse of a pair of stimuli is applied near to or in the vulnerable period of the ventricle, the possibility of development of ectopic beats has been a cause for concern. The frequency of development of ectopic beats was studied at different basic frequencies in the experiment depicted in Fig. 7. The threshold intensity of stimuli required to drive the ventricle with single stimuli of 2 msec duration was found to be 0.8 Ma. At each cycle length ($S_1S_1$) between 400 and 1,000 msec, the ventricle was first driven by single basic stimuli ($S_1$) of 3 Ma; the coupled stimuli ($S_2$) were delivered to the ventricle during the refractory period of the basic responses and the $S_1S_2$ interval was then gradually increased until the ventricle responded to the second stimulus

The $S_1S_2$ interval was then further increased by increments of 5 to 10 msec and the incidence of ectopic activity was recorded. If no ectopic beats occurred, the stimulus intensity was increased in increments of 1 Ma up to 10 Ma and a similar scan with $S_2$ was made at each stimulus intensity until ectopic beats developed. At a basic cycle length of 1 000 msec in 1 spontaneous ectopic beats developed with a stimulus intensity of 1 Ma, well below two times the threshold strength. Ectopic beats occurred with stimuli of 3 Ma at a basic cycle length of 800 msec in *B* and with stimuli of 10 Ma at 600 msec in *C*. No ectopic beats developed after the second stimulated responses with a stimulus intensity of 10 Ma at a basic cycle length of 400 msec in *D*. In this experiment the ectopic beats could not have been propagated from supraventricular sites because the A-V conduction system was completely suppressed by intense vagal stimulation. Evidence for A-V dissociation is seen in the record of atrial responses which occurred at a frequency higher than and independent of the ventricular rate.

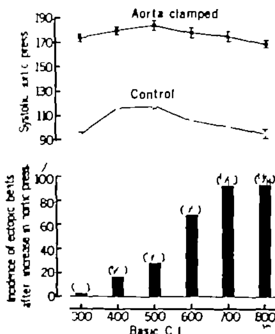



Fig. 4 The ... bat ... from 107 ... ... sort ... to 4 log. The incidence of pre... ... shown in the lower part ... the ... bars (± S.E.) of control and ... pressure ... shown ... the upper part for different ... length

Fig. 6 shows the cumulative data of 8 experiments on paired-pulse stimulation. Ectopic beats occurred after stimuli of 10 Ma or less in 7 of the 8 cases (85 per cent) at a basic cycle length of 1 000 msec. In 2 cases the effective stimulus intensity was less than two times the diastolic threshold value. At higher basic frequencies the incidence of ectopic beats diminished. At $S_1S_1$ = 400 no spontaneous activity occurred in any of the trials.

## Discussion

The results of these experiments are in agreement with clinical observations (card)

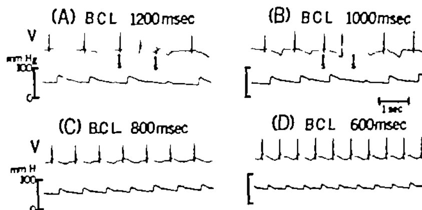



Fig. 5 Exp 7 16-65 Premature ectopic beats developed in the ventricle ... hypothermia at different basic cycle length. The upper traces show ventricular response and the lower traces ... pressure. In some of the upper traces the time of application of ... stimulus ... S

ectopic beats occurred in the ventricle more frequently when the basic rate was relatively slow. This was true whether the precipitating agency was coronary occlusion, sudden elevation of the aortic pressure, or hypothermia.

Han and co-workers[4] demonstrated a greater range of refractory periods at various points on the ventricular surface when the basic frequency was low, and they proposed that early ectopic activity could be the result of re-entrant excitation of already repolarized elements by the flow of current from still depolarized neighboring elements. Other studies also indicate that the difference in refractory periods in ventricular tissues increases as the heart rate decreases. For example, Moe and associates[15] showed that the difference in refractory periods between the bundle of His and the right bundle branch is greater at slow frequencies of the heart, and Moore and co-workers[4] demonstrated that the duration of action potentials and the refractory periods of false tendon, essentially equal to those of papillary muscle at high driving rates, greatly exceeded the latter at frequencies of 1 per second. These observations suggest that the likelihood of the development of re-entrant ectopic activity is enhanced not necessarily within ventricular muscle itself, but perhaps at junc-

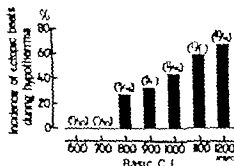



Fig. 6. The cumulative data on the incidence of premature ectopic beats in the ventricle obtained from 183 trials of ventricular driving at different basic cycle lengths in 3 dogs during hypothermia.

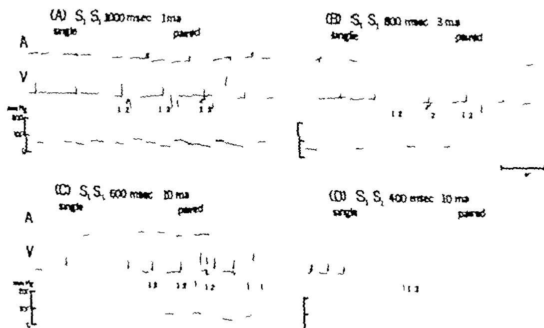



Fig. [illegible] Exp. 8-4-63. Spontaneous ectopic beats developed after the second stimulated responses during paired pulse stimulation at different cycle lengths of basic stimuli ($S_1S_1$). The upper traces show atrial responses, the [illegible] traces show ventricular responses and the lower traces show the aortic pressure. In the middle traces the [illegible] application of the first and the second of a pair of stimuli [illegible] indicated by 1 and 2. The traces obtained during single-pulse stimulation at different [illegible] were also shown for comparison with those during paired pulse stimulation.

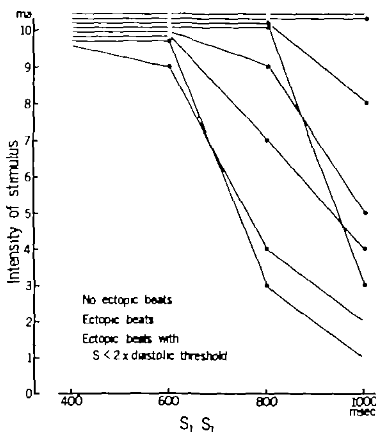



Fig. 8 The data obtained from 8 experiments on paired pulse stimulation. Basic cycle length or interval between two basic stimuli ($S_1 S_1$) is plotted on the abscissa in milliseconds and the intensity of stimuli used to test the occurrence of spontaneous ectopic beat after the second stimulated responses is plotted on the ordinate in milliamperes. Each solid line connecting four different points indicates the results of an individual experiment.

tions between two different tissues, that is *ventricular muscle and the specialized* conduction fibers.

The present studies demonstrate that the hazard of inducing ectopic beats during paired pulse stimulation is increased at slow basic frequencies. Similar findings were reported by Langendorf and Pick.[3] In their clinical observations ectopic beats which were previously present during paired pulse stimulation at a relatively slow frequency could be abolished by increasing the rate of paired pulse stimulation. In the present experiments the stimulus intensity required to induce ectopic beats after the second stimulated responses was lower at low frequencies. In 2 cases the effective stimulus was less than twice the diastolic threshold, a strength reported to be safe.[16] The results are in agreement with those of previous studies in which the ventricular fibrillation threshold was found to be inversely related to the basic cycle length.[4]

Clinical situations requiring electrical stimulation of the ventricle are frequently associated with underlying conditions which may facilitate the induction of ventricular ectopic beats and fibrillation. For example, the presence of irregular perfusion of the ventricle associated with coronary heart diseases is known to contribute to increased asynchrony of recovery of excitability in ventricular muscle.[4] It is particularly important, therefore, to select an optimum rate of stimulation in the presence of these additional contributing factors, and to consider the possible additional hazard involved.

## Summary

The frequency of development of ventricular ectopic beats was studied at different basic frequencies under condition

which facilitate the induction of ectopic beats and fibrillation in the ventricle Ectopic beats were more frequently induced by coronary occlusion sudden elevation of the aortic pressure and hypothermia when the basic frequency was low The average time of onset of ectopic beats after the start of coronary occlusion decreased with a decrease in basic frequency Ectopic beats developed more frequently after the second stimulated responses at slow rates of paired pulse stimulation The stimulus strength required to induce such ectopic beats was much lower at slower frequencies of paired pulse stimulation The results emphasize the importance of selection of an optimum rate of stimulation

We wish to thank Miss Mae Malout and Chalmers Lyons for their technical assistance

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# Body surface isopotential maps in normal children, ages 4 to 14 years

*Madison S. Spach, M.D.**
*William P. Silberberg*
*John P. Boineau, M.D.***
*Roger C. Barr, B.S.*
*E. Croft Long, M.B., Ph.D.*
*Thomas M. Gallie, Ph.D.*
*Judith B. Gabor, M.A.*
*Andrew G. Wallace, M.D.*
*Durham, N. C.*

The ultimate diagnostic potential of electrocardiographic data obtained from the body surface will be realized only after extensive studies have been conducted to define the areas of the body which contain important information. The recent work of Taccardi[1] and Horan, Flowers, and Brody[2] in human beings has demonstrated that the construction of total thoracic electrocardiograms (isopotential surface maps) provides information that is not available in tracings obtained with conventional electrocardiographic and vectorcardiographic lead systems. The major question concerning the clinical usefulness of looking at all of the information available at the body surface, if this can be derived eventually, will be answered only by showing what information proves to be helpful in diagnosis and the management of the patient.

On the basis of the work of several investigators,[1-3] our group has undertaken an interdisciplinary endeavor to develop a practical method for generating isopotential surface maps in children and to develop a library of isopotential maps characterizing normal subjects and children with different cardiac conditions. This report presents (1) a digital computer method for constructing isopotential surface maps, (2) a method for the calculation of zero potential on the body surface during various portions of ventricular activation, and (3) the distribution of the body surface potentials for normal children between the ages of 4 and 14 years.

## Methods

Twenty normal children between the ages of 4 and 14 years were studied. All patients were normal by history, general physical examination, auscultation, phonocardiograms, cardiac x-ray film, elec-

From the Departments of Pediatrics (Division of Cardiology) and Medicine, Duke University [illegible] [illegible] Department of Electrical Engineering and Mathematics, Duke University, Durham, N. C.
This work was supported by United States Public Health Service [illegible] [illegible]
Received for publication [illegible] 1966.
*Address: Department of Pediatrics, Duke University [illegible] Durham, N. C. 27706.
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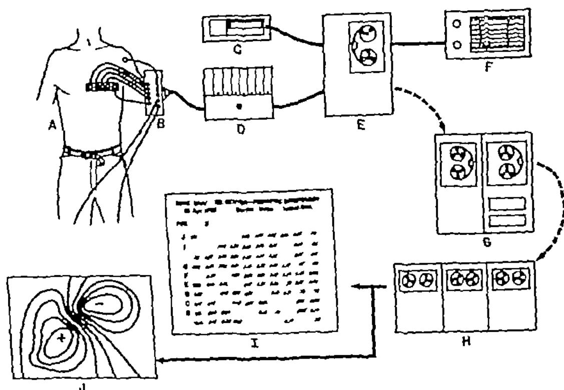



Fig. 1. Schematic representation of the techniques of acquisition and processing of data for the construction of isopotential surface maps. A, Patient and lead connections. All children were studied in the supine position. Five thoracic electrocardiograms were obtained simultaneously in reference to the left leg electrode. After a block of 5 points were recorded the electrode assembly was moved to a new position and this sequence was continued until 150 to 250 points had been recorded over the entire thorax. All thoracic electrocardiograms were recorded simultaneously with a reference lead. An impedance respirometer was used to record respiration and only complexes occurring during resting expiration were analyzed. B, Buffer system. This unit prevented distortion of wave form and amplitude due to varying skin-electrode impedance contacts. C, Time-code generator. A time-code signal was generated during the tape recording of all electrocardiographic data. The time code was used for editing purposes to localize data on tape for analog-to-digital conversion. D, Amplification system. The high-gain AC amplifiers were part of an Ampex data acquisition system. E, Tape recorder. Six channels of electrocardiographic information and the time code were recorded simultaneously. While the data were being tape recorded the output of the tape recorder was fed to a graphic recorder (F) to determine that technically good data were being obtained. G, Analog-to-digital converter. Once editing had been performed the data on tape were transcribed by an analog-to-digital converter at a digitizing rate of 226 samples per second per channel. H, IBM 7072 digital computer. The digital tapes were processed by the computer and the voltages of all leads were measured in reference to the base line (T-P segment) every millisecond. I, Computer output. The final output was programmed in a format such that the individual voltage values at 1 msec. interval were printed out spatially to correspond in position to the individual lead placed on the body surface. Also the maps were processed for the automatic construction of individual maps (J) by a Calcomp plotter.

trocardiograms and vectorcardiograms (Frank system) were interpreted as being normal.

*Introduction of isopotential maps*

A. DATA ACQUISITION METHODS. A schematic representation of the data acquisition and processing system is shown in Fig. 1. All patients were studied in the supine position. To explore the entire thorax, a grid system was marked over the upper abdomen and thorax to record from 150 to 250 points (Fig. 2). The distance between the explored points was 2.5 to 3.0 cm. over the anterior and lateral chest surface; over the back the distance between the points was 2 to 3 cm. vertically and 4 to 5 cm. horizontally. The chest electrodes were gold-plated brass plates 7 mm. in diameter. Each electrode assembly consisted of a modification of the electrode developed by Dr. Lorin Angier of the University of Tennessee

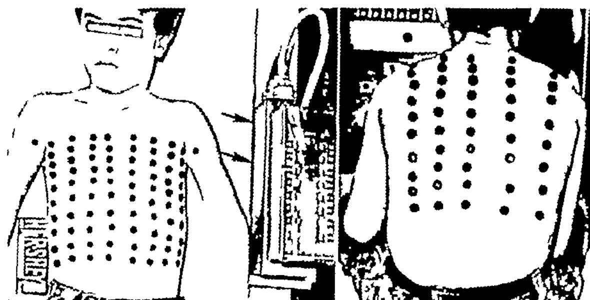


Fig. 2. Grid system used for electrode placement for recording 150 points over the entire thorax. In the smaller children the isopotential surface maps were constructed from 150 points. In children over 10 years of age 250 points were utilized. After the child was made to feel at ease in the laboratory, a washable paint was used to construct the grid. The arrows point to the buffer unit which provided for impedance matching of the individual leads. Notice that the interelectrode distance is approximately twice as great for the back as for the anterior thorax. In calculating the zero area for the isopotential maps, the numbers for each point were weighted according to the area they represented (*see Appendix*).

School of Medicine. A small layer of electrode cream (EKG Sol) was applied to each electrode. There was no cream outside each electrode border. To avoid skin-electrode impedance variation producing *loss of amplitude or distortion of the wave form* of the tracings, the recording system included individual lead impedance matching and isolation through a buffer system.[8] The buffer system contained a unity voltage gain input impedance amplifier between each electrode and the recording system input. These buffer amplifiers have an input impedance greater than 50,000,000 ohms and an output impedance of less than 10 ohms.

With the use of an Ampex Data Acquisition System 100, five tracings from the body surface were simultaneously recorded using a common left leg reference point. The technician held an array of five electrodes on an elastic band against the chest while a block of five points was recorded. After the block was recorded, the procedure was repeated in a new position until all points were explored. Together with each group of five tracings an additional time reference lead was recorded. This lead was chosen by placing an electrode on the thorax (referenced to the left leg) in a position so that the QRS complex *produced a biphasic deflection*. The entire procedure required approximately 2 hours. At the completion of the study each patient was photographed and the lead placement for the Frank vectorcardiogram and conventional electrocardiogram was noted.

All data were recorded on magnetic tape. The entire system was found to have a frequency response flat to 5,000 cycles per second. The noise level varied from 0.015 to 0.05 millivolts (peak to peak) with the electrodes attached to the patient (Fig. 3). The seventh channel of the tape was utilized to record the output of a time code generator. While data were recorded on tape, the tape output was monitored by a Honeywell Visicorder 1508 oscillograph in order to edit the data for digital computer analysis. An impedance meter was used to monitor

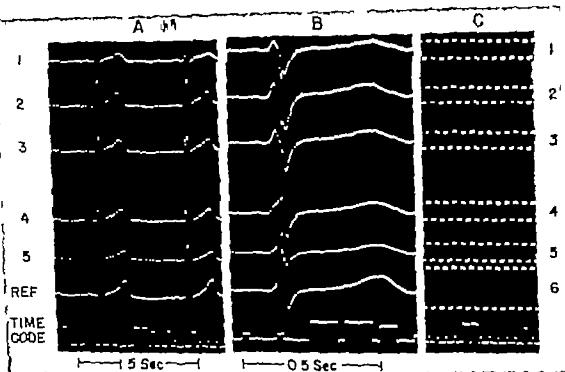



Fig 3 Graphic readout obtained during *recording of data* The upper five tracings represent recordings over the chest from five adjacent points while the reference lead was recorded simultaneously The seventh channel of the tape recorded and reproduced the time-code signal which was utilized for editing and localizing on tape the exact complex to be processed by *the analog to-digital converter for computer analysis* Immediate visual inspection was available by reproduction from tape of the complexes recorded at relatively slow paper speed (*A*) More rapid paper speed (*B*) were used *to better detect noise and/or artifacts* Calibration of each lead is shown in *C*

respiration only beats which occurred during resting expiration were analyzed

B DATA PROCESSING METHODS The *oscillographic* data were reviewed and the proper beats chosen for analysis By noting the complex to be analyzed in *reference to the time code* the data then were processed automatically *for* input into an IBM 7072 computer An Airborne *Instrument* Laboratories analog to digital converter sampling at a rate of *926* samples per second processed the data for input into the computer

Through use of the wave identification program of Caceres and co workers[9] the computer identified the QRS complex and defined the base line *in the* P R segment for the reference lead The time of the base line crossing of the intrinsecoid deflection of the QRS was used for time localization Voltage in all *of the tracings* were determined at 1 08 millisecond intervals throughout QRS Repeated checks of computer output indicated that time *localization* was accurate within ±1 08 milliseconds More rapid digitizing rates (*e g 1 852* samples per channel per second) produced no apparent change in the final isopotential maps

Since the voltage at the left leg varies throughout QRS the zero voltage for each instant of time for the body surface was calculated from the total thoracic voltage distribution by averaging all measurements with appropriate weighting factors (see Appendix) The output was presented for 1 08 millisecond intervals in a format which represented the thoracic distribution of the body surface voltage Finally another set of maps was automatically constructed by a Calcomp plotter (Fig 4) From 60 to 110 isopotential maps were constructed for each subject

*II Correlation of surface event with*

Fig. 4. Instantaneous surface map produced by the [illegible] Calcomp plotter. The surface maps were calculated by the computer and the [illegible] isopotential lines of equal voltage using linear interpolation. The dotted line indicates the calculated zero [illegible]. The maximum (+) and minimum (−) are designated accordingly. The potential difference between lines for this map is 0.2 mV for the [illegible] and 0.1 mV for the [illegible] line. The numbers [illegible] printed and represent numbers designating positions on the [illegible]. ([illegible] computer program [illegible] to accomplish the plotting.)

*right ventricular epicardial activation sequence.* Two patients with congenital aortic valvular stenosis and another with a ventricular septal defect underwent direct right ventricular activation studies at the time of cardiac surgery. Although these patients did not have *normal* hearts, the right ventricular pressures were normal and the isopotential surface maps through the first 30 milliseconds were similar to those obtained from normal children. Bipolar tracings were obtained from twenty areas over the right ventricular free wall. *The recording electrode consisted of contacts* placed 2 mm apart. Lead II or III was recorded simultaneously as a time *reference*. The epicardial electrogram and ECG signal were amplified with Tektronix 122 preamplifiers, *recorded on an* Ampex SP 300 tape system and later recorded on a Consolidated oscillograph at a paper speed of 400 mm per second. For each tracing, the apex or base line crossing of the intrinsic deflection was used to determine the time of local activation at each epicardial area. These points in turn were related *in time to a sharp* deflection point on the reference ECG. These data were used to construct maps of the sequence of epicardial excitation. Observations in these 3 patients provided a *means for relating* voltage changes at the body surface with the sequence of activation of the human right ventricle. The maximal timing error in relating events on the epicardial surface with the isopotential body surface maps was considered to be ±2.5 milliseconds.

**Results**

In discussing the body surface voltage distribution, the terms employed by Taccardi will be used. A potential *maximum* is *a region on the body surface* where the voltage is higher than in the neighboring regions. A potential *minimum* indicates a region where the potential is lower than in the surrounding region. Seventeen of the 20 children demonstrated a similar sequence of changing events on the body

surface as shown in Figs 5 and 6 Although there was variation in the distribution of isopotential lines among the subjects there was a consistent pattern which demonstrated six major events as follows

*1* The first indication of ventricular activation was the development of a relatively small maximum over the sternum anteriorly with a minimum at the left anterior axillary line or in the mid axilla (Fig 5 4) The position of this early

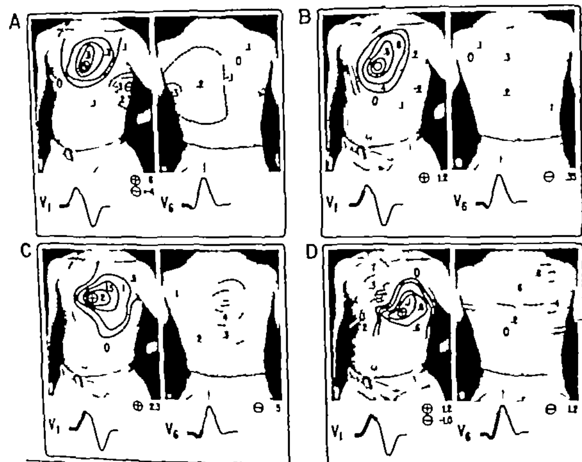



Fig 5 Isopotential surface maps in a normal 8 year-old child The sequence demon trated f QRS is illu tra tiv of most of the children stu lied It hould be empha ed th t many minor lifferen es we e found mong the subjects of the normal group h wever the *general* pattern hown w con tent mon the l je t tud ed The whit line in l cates the cal ulated zero line the solid l nes denote pos ti k es nd th da hed lines l cate negative aloes The + and − s gn denote the h hest (maximum) l lowest (m num) ltage areas respecti ely l During the earliest tage of entricular acti tion the d t butio w dipola with small circumscribed max mum over the central anterior che t and the minim locat d the left axill Th w associated with the onset of the R wa e in Lead V nd Q w f Le l V *B* W th the ri e f the R wa e in Lead V an l the complet on f the Q w in Le l V the ce tral t m xim m e larged and was a sociated with a rap d *h ft* f the m nimum t the centr l back C There fter the mum ncreased w th pseud pod extens on nferiorly down over the l ft prec dium wh h the m m m rema d in the central upper ba k *D* O er period of 5 t 8 msec pseudopod exten occurred in th rea of the maximum shown in C w th the sud len emergence of discrete mall m nimum (−) over the central ternum w th nother mini mum over the ght shoulder These two minima were ep t ted by area f rel tiv ly greater oltage— described by Taccardi a sa lle D ring these ents the max um h fted l htl t the left nd down er the left precord um D rect ght ent l r epe rdial t t t le l ted th t the development f the d scr t m m m h w V tl central t num w l t l t ht tru l ep cardial break thro gh l m area (l t ) parent t t s of the right t l nd e (S *l F* 6)

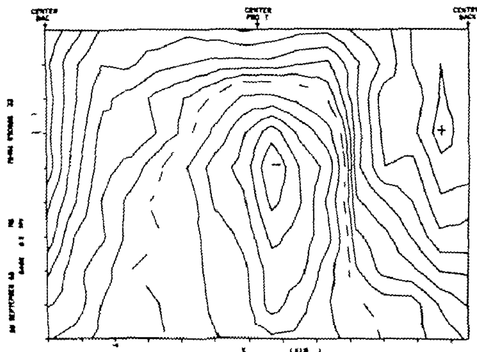



Fig. 4 Instantaneous surface map produced by Calcomp plotter. The surface maps were calculated by the computer and then plotted ... lines of equal voltage ... The dotted line indicates the calculated zero ... The maximum (+) and minimum (−) are designated accordingly. The potential between lines for the map ... 0 m ... for the ... and 0.1 m for the positive ... The numbers ... 10 ... printed and represent numbers designating positions on the ... the computer program designed to accomplish the plotting.)

right ventricular epicardial activation sequence. Two patients with congenital aortic valvular stenosis and another with a ventricular septal defect underwent direct right ventricular activation studies at the time of cardiac surgery. Although these patients did not have normal hearts, the right ventricular pressures were normal and the isopotential surface maps through the first 30 milliseconds were similar to those obtained from normal children. Bipolar tracings were obtained from twenty areas over the right ventricular free wall. The recording electrode consisted of contacts spaced 2 mm apart. Lead II or III was recorded simultaneously as a time reference. The epicardial electrogram and ECG signal were amplified with Tektronix 122 preamplifiers, recorded on an Ampex SP 300 tape system and later recorded on a Consolidated oscillograph at a paper speed of 400 mm per second. For each tracing, the apex or base line crossing of the intrinsic deflection was used to determine the time of local activation at each epicardial area. These points in turn were related in time to a sharp deflection point on the reference ECG. These data were used to construct maps of the sequence of epicardial excitation. Observations in these 3 patients provided a means for relating voltage changes at the body surface with the sequence of activation of the human right ventricle. The maximal timing error in relating events on the epicardial surface with the isopotential body surface maps was considered to be ±2.5 milliseconds.

## Results

In discussing the body surface voltage distribution, the terms employed by Taccardi[1] will be used. A potential *maximum* is a region on the body surface where the voltage is higher than in the neighboring region. A potential *minimum* indicates a region where the potential is lower than in the surrounding region. Seventeen of the 20 children demonstrated a similar sequence of changing events on the body

3 The distribution changed rapidly with the minimum shifting in all children to the right scapula or upper mid back on the posterior surface with concomitant increasing negativity anteriorly over the right upper chest under the clavicle Coincident with these events and immediately thereafter pseudopods enveloping negative voltage projected into the area of the mid sternum anteriorly These pseudopods encroached upon the area surrounding the maximum either from the right upper chest or from a direct superior direction down inferiorly toward the central sternum

The development of pseudopods occurred over an interval of 5 to 8 msec and was followed by the rapid emergence of another area of negativity in the central upper sternum (this area later became the principal minimum) At this instant of time (Fig 5,D) the surface voltage distribution was nondipolar and was quite characteristic of the distribution described by Taccardi[1] in adults with two potential minima (central sternum and right shoulder) and a saddle encompassing an area of relatively higher voltage interposed between the two minima During these changes the maximum shifted slightly to the left over the precordium from its original central location These events correlated with inscription of the peak of the R wave in Lead $V_1$ The development of the two minima and saddle over the anterior chest occurred 20 to 28 msec from the onset of initial activity on the body surface

4 5 There was considerable variation in the configuration of the isopotential maps describing the ensuing interval however Fig 6 *E* and *F* present characteristic changes which occurred during inscription of the intrinsicoid deflection in Lead $V_1$ and onset of the intrinsicoid deflection in Lead $V_6$ In all patients this period was characterized by gradual enlargement of the anteriorly located minimum Together with the increasing magnitude and size of the anteriorly located minimum there was the development of pseudopods from the maximum in a leftward direction posteriorly to the upper or lower axilla These events occurred over varying periods of time (7 to 21 msec) In one child two minima (one over the right lower chest and another over the left anterior axillary line) developed transiently Ultimately the maximum shifted to the left axilla while the area surrounding the minimum enlarged to cover most of the anterior chest

*6* The remaining period of ventricular activation (17 to 30 msec) was similar in all but 3 subjects The characteristic sequence is shown in Fig 6 *G* and *H* The minimum enlarged anteriorly while the maximum shifted to the central back During the final 5 to 10 msec the anterior minimum fragmented and the maximum over the central back disappeared In several of the children the separation of the end of ventricular activation from the onset of the S T segment was difficult because of the development of a small maximum (0 1 to 0 15 mv) over the mid left chest The maximum persisted during the inscription of the S T segment and showed further enlargement with the development of the T wave

In 2 subjects the posterior maximum was accompanied by an additional maximum located over the upper central sternum and a minimum over the lower sternum during the last 15 to 25 msec of ventricular depolarization (Fig 7,*A*) In 1 patient there was an anterior centrally located maximum with two precordial minima one on either side of the maximum (Fig 7 *B*)

## Discussion

*A Limitation of methods* Precise documentation of the contour lines of cardiac potentials over the body requires (1) accurate time localization within complexes recorded from multiple points at different times and (2) knowledge of the noise level present in the final digital computer output in order to determine what is a significant change in voltage

Through the choice of a reference tracing which was biphasic in form timing between various points recorded at different times was within the limits of ± 1 08 msec in the final output Two subjects were mapped twice in order to determine the reproducibility of the results Each pair of outputs showed excellent agreement

During the recording of multiple points

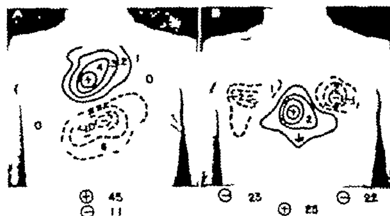



Fig. 7 Surface potential distribution over the anterior chest during terminal QRS found in 3 children. 1. In two children the terminal distribution of surface potential was characterized by a maximum in the central back with an additional maximum over the upper central sternum as shown. The minimum was located over the left lower precordial region. B In one child terminal ventricular activation was characterized by a posterior maximum with additional centrally located anterior maximum with two minima situated on either side of the maximum. The surface potential distribution at the end of the QRS shown was suggestive of wave fronts located in the anterior septum and posterior ventricular

over the body individual electrodes occasionally demonstrated noise not present in the remainder of the tracings. This was especially true over the upper abdomen and right pectoralis muscle. Such noise usually was muscle tremor and was eliminated by perseverance on the part of the investigator in working with the children by repeating tracings obtained from the same block until technically good data were produced. Constant observation of the tape output while data were being accumulated provided visual checks to ensure a minimum noise level in the originally recorded data.

*B. Potential information in isopotential maps.* The isopotential maps in the children studied showed more nondipolar surface distribution than found by Taccardi in adults. This may be related to the more frequent sampling of events, the enhanced proximity effects which are present in smaller subjects, or a boundary configuration which in children is different from that in adults.

The recorded surface maps showed six major events. On the basis of the work of several investigators,[4,1] the time course of these events suggested corresponding events of ventricular excitation. Furthermore, several of these events were confirmed by direct measurements on the surface of the right ventricle. The major events were the following:

*1.* The initial development of an anterior central maximum and *left* axilla minimum (Fig. 5 *A*) was probably due to the predominant wave front invading the left septal surface.

*2.* During the following stage, with the shift of the minimum posteriorly and enlargement of the maximum over the central sternum, the contours of the body surface potential were predominantly dipolar in nature (Fig. 5 *B* and *C*). This interval suggested invasion of the ventricular free walls with the major wave front becoming oriented in an anterior posterior direction.

*3.* Immediately *following* this, the distribution became nondipolar with the minimum shifting to the right scapular and upper right chest anteriorly and with the invasion of pseudopods over the sternum anteriorly. The midsternal region rapidly developed a minimum which was separated by a saddle from the right shoulder potentials (Fig. 5 *D*). As suggested by Taccardi[1] this most likely reflected epicardial breakthrough of wave fronts in the right ventricular free wall. Direct evidence that such is true was obtained in 3 children undergoing cardiac surgery; however, the relationship was found to be more complex than the simple

occurrence of epicardial breakthrough. These children with normal right ventricular pressures demonstrated a normal sequence of epicardial activation over the right ventricular free wall as found by Wallace and associates.[14] The earliest time of epicardial breakthrough in the 3 patients studied occurred 5 to 7 msec before the development of the discrete minimum over the midsternal region. The initial development of pseudopods which would later emerge as the discrete minimum correlated best in time with the breakthrough of activation in the right ventricular free wall. From measurements of the sequence of epicardial spread over the right ventricle it was estimated that an area of 1.0 to 2.0 square centimeters of epicardial breakthrough had developed when the discrete minimum emerged over the central sternum with its adjacent middle (Fig. 5 *D*).

4 The enlarging minimum over the upper anterior chest correlated with the epicardial wave front completing its spread over the right ventricle (Fig. 6 *E*).

5 The subsequent shift of the maximum from the left anterior precordium to the left axilla and back (Fig. 6 *F* and *G*) suggested epicardial breakthrough of wave fronts in the anterior left ventricle while depolarization continued over the left lateral and basal left ventricular free wall.

6 The final phase of ventricular depolarization (Fig. 6 *H*) was characterized in most children by an anteriorly located minimum with a maximum over the central back. This suggests continued activation in the posterior basal left ventricular free wall and septum. In 3 subjects this terminal phase was characterized by an additional maximum over the upper central chest with a pattern similar to that found by Taccardi in several adults.[1] The anteriorly located maximum in these subjects suggests late activation wave fronts in the upper anterior septum and/or crista supraventricularis.

## Summary

A method is presented for the production of isopotential surface maps in children. After recording from 150 to 200 points over the body, the data were processed for analysis by a digital computer with the output of an instantaneous surface map for approximately every millisecond. The presence of dipolar and nondipolar distribution of body surface potentials varied throughout QRS; however, the children demonstrated considerably more of a nondipolar distribution than found by Taccardi in adults. Direct evidence was obtained relating the development of a central minimum over the sternum to epicardial breakthrough of wave fronts in the right ventricular free wall. These studies add emphasis to the need for the further accumulation of data in patients with normal and abnormal hearts to define the time course and location of electrical events on the body surface since important information is available in areas not sampled by conventional electrocardiographic lead systems.

## Appendix

*A method for deciding the zero line in isopotential surface maps*

When measuring the distribution of chest potentials on the surface of the body there is considerable advantage in recording each of the potentials against a constant reference point. In particular, if the potential at the reference point does *not* change from instant to instant, then the line designated "A" mv on the map for 1 msec corresponds to the line marked "A" mv on the maps for all other instants. However, if the potential at the reference point *does* change from instant to instant, then the lines do not necessarily correspond.

If the heart consisted of a single dipole generator throughout the sequence of its activation, it would in principle be easy to measure points on the chest against a constant reference. The reference point would be the center of the dipole, i.e., inside the body torso. Since the heart is not a physical dipole (even though it produces some dipole-like effects) and since the interior points are not accessible as reference points, a practical reference point must be some point or a combination of points on the surface.

If the reference used is a single electrode on the surface, the reference point's potential changes with time. As the heart activity moves toward the point

reference point become more positive, and when the cardiac activity on the whole moves away from the reference point, the reference point becomes relatively negative. On the other hand, if the reference is the average of a widely separated combination of points, then the reference is more nearly constant. One such combination is the Wilson central terminal. The average of the points of the central terminal provides a more nearly constant reference because, when the potential of one rises, the potential of another is likely to fall; thus the average remains about the same.

In order to facilitate the recording, construction, and interpretation of isopotential maps at varying instants of time, various reference systems were evaluated against these criteria: (1) convenience of recording and data processing, (2) applicability to surface maps previously recorded utilizing reference points at the left leg and Wilson central terminal, and (3) representation of the net electrical effects of the heart at points on the surface by positive and negative areas of the potential distribution. Gelertner and Swihart[14] have proposed a digital computer simulation scheme for evaluating the potentials produced on the surface of a volume conductor by internal current generators. Additionally, Selvester and co-workers[15] have utilized digital computer techniques for simulation of the peripheral vectorcardiogram. In this study, the method of Barr and associates[16] was used to estimate the zero line distribution utilizing four different reference methods. The purpose of the evaluation was not to add to the studies and theories of Bayley[17,18] and Brody[19] regarding zero lines, but rather the purpose was to decide which of the proposed systems seemed both to give good answers in simulated problems and to be practical for surface map processing, while at the same time being a reasonable extension of related theoretical ideas.

With the use of an IBM 7072 computer, three groups of dipoles were arranged

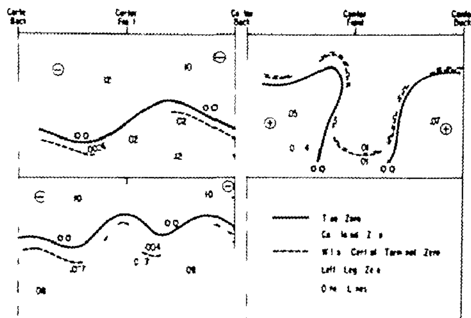


Fig. 2. Comparison of zero lines produced by different reference systems. The surface distribution maps were derived by the method of Barr and associates, utilizing a digital computer simulation program to arrange three groups of dipoles (each group containing approximately ten dipoles) inside a cylindrical boundary. Each of the three maps shows the distribution of potential for one group. The distribution of the zero lines utilizing different reference systems is presented in comparison to "true" zero as produced by three internal generator configurations. Other lines represent isopotential lines of varying values distributed over the cylinder boundary.

made a cylindrical surface boundary. The computer calculated the surface potential distribution referenced to the dipole centers. Once the surface potential distribution was derived, four isopotential lines were compared. These represented the lines that would be called zero lines for references consisting of the dipoles center, the left leg, the Wilson central terminal, and the average of all voltages.

Fig. 5 illustrates the results and shows the various lines that would be marked zero with the different reference systems used. The left and right edges of each map represent the center of the back of the cylinder. The "true" line is the zero potential referred to the dipoles centers. Note that the zero derived by averaging all voltages on the surface represents a close approximation of the "true" zero. The lines for the Wilson central terminal zero showed further separation from "true" zero, whereas the left leg zero showed the greatest deviation of the *methods* evaluated. Notice that although the lines marked "true" are at approximately the same voltage on each map, the other lines are not. That is, the "true" line has a consistent meaning with respect to the net generator activity in all three maps, whereas the use of the left leg or Wilson central terminal reference system produced lines whose relationship to the net generator activity changed from map to map. In short, by averaging the voltages over the walls of the cylinder, giving equal areas equal weights, a close approximation to "true" zero was achieved.

Since the foregoing results indicated that a close approximation of "true" zero could be obtained by averaging with proper weighting the values over the entire surface, a similar program was designed for application to the isopotential maps recorded in patients. Originally, the data were recorded with the left leg as reference. The main advantage of recording the thoracic potentials in reference to the left leg is that greater voltage values are recorded than when the Wilson central terminal is used. This affords a larger signal-to-noise ratio in the original data. The data are processed by the digital computer, and in this process surface maps are derived. The numbers are then weighted according to the area that they represent, i.e., the anterior lateral thoracic points are weighted by a factor of 1 and those on the back are weighted by a factor of 2. (As shown in Fig. 2, the area sampled by each electrode on the back was approximately twice that of each point on the anterior lateral thoracic surface.) The average value derived is then designated as "zero." Thereafter, all of the points are recalculated; the new value at a point is the old value minus the derived zero.

An additional advantage of producing isopotential maps by this method is that it allows the comparison of maps derived in various laboratories regardless of the "zero" reference point used. Since there is increased interest in this problem in many laboratories, standardization of "zero" calculation may prove to be quite helpful in the future for uniformity of interpretation among different investigators.

We would like to express our appreciation to Dr. D. A. Brody, Department of Medicine, University of Tennessee School of Medicine, Memphis, Tenn., for his helpful suggestions which led to the final development for the method of calculating the zero voltage distribution on the body surface. We also would also like to thank Dr. Bruno Taccardi of the Instituto di Cardiologia Sperimentale, Milan, Italy, for the privilege of reviewing his movie concerning isopotential surface maps in adults with normal and abnormal hearts and for his free exchange of ideas related to isopotential surface mapping. Also our close communication with Dr. Ronald H. Selvester, Rancho Los Amigos Hospital, Downey, Calif., has been most helpful. Finally, we should like to acknowledge the most valuable technical assistance of Mr. Stanley Greenway and Mr. James Graham, Jr., for their patient attention to detail during the acquisition and processing of data.

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# The relationship between the timing of atrial systole and the useful work of the left ventricle in man


*Robert E. Snell, M.D.**
*Peter C. Luchsinger, M.D.***
*Gerald I. Shugoll, M.D.****
*Washington, D. C.*


The prominent phasic variations in arterial pressure noted in patients with an idioventricular cardiac rhythm have been related to alterations in the temporal relationship between atrial and ventricular contraction.[1] Presumably, accompanying changes occur in the left ventricular volume output and in the useful stroke work. It has not been possible to quantitate these changes in man, however, with methods previously available.

The computed pressure gradient technique has recently been applied to the measurement of instantaneous blood flow in the human ascending aorta.[2] If aortic end-diastolic flow is assumed to be zero, the volume output of the left ventricle can be estimated for individual beats. Such estimates together with measurements of instantaneous aortic pressure have been used to calculate left ventricular work and power in man under various conditions.[3] The present report extends these observations to 3 subjects with acquired chronic complete heart block of unknown etiology. The patients were studied during idioventricular pacing and the results were analyzed to determine the effect of variations in the timing of atrial systole on useful ventricular work and power.

#### Method

The patients were studied at rest without premedication. All had acquired complete heart block and were judged to be suitable candidates for implantation of an artificial pacemaker. Prior to the actual operation an electrode catheter† was passed into the right ventricle and set to produce a stimulus rate near 60 beats per minute. The R-R and P-P intervals in each subject are shown in Table I. A specially designed dual-lumen catheter‡ was then introduced through the surgically exposed femoral artery and advanced to the ascending aorta just distal to the aortic valve.


From the Cardiopulmonary [illegible] Veterans Administration Hospital, [illegible] Georgetown University School of Medicine, Washington, D. C.
Received for publication Jan. 17, 1966.



*[illegible] Veterans Administration [illegible] Georgetown University School of Medicine [illegible] Veterans Administration Hospital, [illegible] Street N.W., Washington, D. C. 20422.
**Chief, Cardiopulmonary [illegible] Veterans Administration Hospital [illegible] Georgetown University School of Medicine.
***Chief, Cardiology Section, [illegible] Veterans Administration Hospital [illegible] Professor of Medicine, Georgetown University [illegible]


†(Model 351) [illegible] Corp. [illegible]
‡U.S. Catheter [illegible] Corp. [illegible]

Measurements of instantaneous pressure, velocity, and flow were then made as previously described.[3] In one patient the pacing frequency was increased and measurements were repeated at a second rate.

Recordings of pressure and velocity (flow) were displayed on a photographic recorder* together with Lead II of an electrocardiogram at a paper speed of 200 mm. per second. An average of 50 paired pressure and flow complexes were then selected at random for analysis in each subject. Ordinate values were measured at 1 mm. intervals by a Gerber automatic scanner† with punch card output. Left ventricular stroke work and power were then calculated from Equation 1 using digital computation.

$$LVSW = \left(\int_{t}^{t} PQdt + \int_{t}^{t} \frac{\rho Qv^2}{2g}\,dt\right)/100 \quad (1)$$

where LVSW is left ventricular stroke work (Gm. M. per beat); P is instantaneous aortic pressure (cm. $H_2O$); Q is instantaneous aortic blood flow (c.c./sec.); v is instantaneous aortic blood velocity (cm./sec.); ρ is blood density (taken as 1.057 Gm./c.c.); g is the force of gravity (980 cm./sec.²); and $t_1$-$t_2$ is the systolic ejection period (sec.). The aortic cross-sectional area necessary to convert velocity to flow was obtained from measurements of the average vessel radius as determined by angiography.[4]

Values for pressure, stroke volume, and stroke work in each subject were then grouped and averaged according to the associated P-R interval; group a consisted of beats with an interval between 0 and 0.09 sec., and group b consisted of those with an interval between 0.10 and 0.19 sec., etc. The seventh group consisted of beats with a P-R interval greater than 0.60 sec.

**Table I.** *R-R and P-P intervals in patients studied*

| Subject | Age (yr.) | R-R interval (sec.) | P-P interval (sec.) |
|---|---|---|---|
| 53 | 69 | 1.010 | 0.680 |
| 63 | 63 | 1.005 | 0.590 |
| 81 | 53 | 1.005 | 0.600 |

## Results

The gross beat-to-beat changes in pressure, flow, and stroke volume found in one patient are shown in Figs. 1 and 2. At a pacing rate of 60 beats per minute (Fig. 1) there are variations in both peak and mean aortic pressure. The peak flow values remain relatively constant at this rate, however, and the changes in stroke volume (the area under the flow curve) result from beat-to-beat differences in the ejection time. At a rate of 105 beats per minute (Fig. 2) there are more prominent variations in both peak and mean pressure and flow.

Average mean systolic pressure, stroke volume, and stroke work in each patient at rates near 60 beats per minute are shown in Table II, and the relationship between the P-R interval and the useful work is illustrated in Fig. 3. Work maxima are seen in each subject, in two when the interval is between 0.10 and 0.19 sec., and in the third when it is between 0.20 and 0.29 sec. Beyond this optimum time, pressure and stroke volume both diminish, with work output decreasing an average of 20 per cent from the peak value. Further lengthening of the P-R interval, however, does not significantly alter the work done until the time exceeds 0.60 sec. At this limit, when the atrial contraction would be expected to have occurred during the preceding ventricular systole, a further drop in external work is seen in the two patients with the slower atrial rates.

The effect on this relationship of an increase in the pacing rate is shown in Fig. 4. Comparison with values for the same individual in Fig. 2 shows that the work done at any given P-R interval has diminished. Most striking at the higher rate is the almost 100 per cent drop in the work accomplished when the interval exceeds 0.30 sec., and there is no effective atrial contraction during the preceding ventricular diastole.

*Model 150, Sanborn Co., Waltham, Mass.

†Model GDDR-3R, Gerber Scientific Instrument Co., Hartford, Conn.

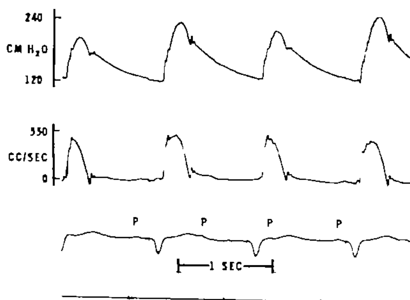



Fig 1 Measurements of pressure flow and Lead II of an ECG made in one subject (No 53) in the ascending aorta during transvenous cardiac pacing at a rate of 60 beats per minute

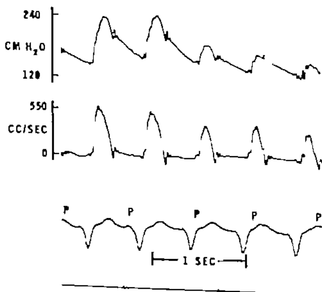



Fig 2 Measurements made in the same individual as in Fig 1 during pacing at a rate of 10 beats per minute

The difference between two consecutive beats in the temporal pattern of work performance is shown in Fig 5 During the early portions of the ejection period power output is about the same in both beats At the shorter P R interval however there is both a marked increase in values for instantaneous power output in late systole and a prolongation of the ejection period resulting in a larger total work output

**Discussion**

Many investigators using various experimental models have confirmed the importance of an appropriately timed

*Table II. Average stroke volume, mean systolic pressure and stroke work at different P-R intervals*

| Subject | | P-R interval (sec) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 0.0-0.09 | 0.10-0.19 | 0.20-0.29 | 0.30-0.39 | 0.40-0.49 | 0.50-0.59 | >0.6 |
| 51 | SV | 5[illegible] | [illegible]8 | 58 | 55 | 5[illegible] | 50 | 4[illegible] |
| | MSP | 1[illegible] | 1[illegible] | 1[illegible] | 1[illegible] | 1[illegible] | [illegible] | [illegible] |
| | LVSW ± SEM | 82 ± 4 | 1[illegible] ± [illegible] | 10[illegible] ± [illegible] | 10[illegible] ± [illegible] | 10[illegible] ± [illegible] | [illegible] ± 5 | [illegible] ± [illegible] |
| 65 | SV | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | |
| | MSP | [illegible] | [illegible] | [illegible] | [illegible] | | [illegible] | |
| | LVSW | 150 ± [illegible] | 151 ± [illegible] | 1[illegible] ± [illegible] | 145 ± [illegible] | 1[illegible] ± [illegible] | 14[illegible] ± [illegible] | |
| 81 | SV | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | 44 | [illegible] |
| | MSP | [illegible] | [illegible] | 71 | [illegible] | [illegible] | [illegible] | 45 |
| | LVSW | 1[illegible] ± 8 | 145 ± [illegible] | [illegible] ± 10 | [illegible] ± 11 | [illegible] ± 5 | 115 ± [illegible] | 90 ± 4 |

[illegible]

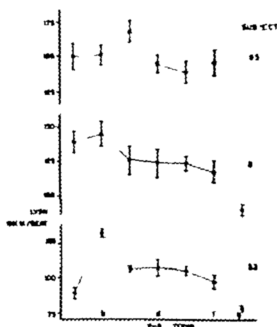


FIG. 3. Left ventricular stroke work as a function of the preceding P-R interval in 3 subjects with complete heart block during temporary cardiac pacing at rates near 60 beats per minute. In each subject individual values for stroke work were first grouped according to the associated P-R interval as follows: *Group a—P-R interval* 0-0.09 sec; *b*—0.10-0.19 sec; *c*—0.20-0.29 sec; *d*—0.30-0.39 sec; *e*—0.40-0.49 sec; *f*—0.50-0.59 sec; *g*—> 0.60 sec. The grouped values were then averaged for each patient. The vertical lines represent the standard error of the mean.

atrial contraction to the subsequent ventricular systole.[1, 8] The extent of this atrial contribution is conditioned by the state of the myocardium and is more pronounced in individuals with congenital heart block than in those with acquired disease.[9] The results of the present study indicate that useful ventricular work may vary from beat to beat by as much as 100 per cent depending upon the presence of an atrial contraction, its placement in time and the cardiac rate. The actual variations are probably even greater since average vessel radius was used in determining blood flow in these studies and changes in aortic diameter were not taken into account.

Of interest is the finding that ventricular work does not fall off progressively as the interval between atrial and ventricular contraction lengthens. Once the optimal P-R interval is exceeded, the useful work output is not significantly lessened by a further lengthening of the interval as long as the atrial contraction falls within the diastolic filling period. When atrial contraction is simultaneous with the preceding ventricular systole, however, there is a further drop in the work accomplished. A possible explanation for this finding can be offered. It is known that left atrial contraction influences both ventricular filling

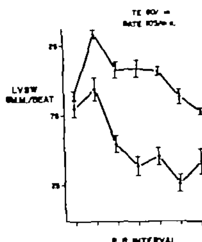



Fig 4 Left ventricular stroke work as a function of the preceding P R interval in one subject at two different pacing rates Work values were grouped and averaged as in Fig 3

and mitral valve closure [1, 13] Probably the occurrence of atrial systole in early ventricular diastole is relatively ineffective with regard to the former effect but still aids in valve closure and limits regurgitation When atrial action is completely absent however both decreased filling and delayed valve closure could result in a further lessening of the useful work accomplished Simultaneous measurements of left atrial pressure would be necessary to verify this

One practical point arises from the variations in stroke volume found at different P R interval If the relationship between the P P and P R intervals is such that beats both with and without an atrial effect occur within short intervals of time repeated measurements of mean cardiac output at the same heart rate should be similar However if the relationship between the intervals is such that a long series of beats with effective atrial contraction is followed by another series without an atrial effect determinations of mean flow would be highly dependent on the time of measurement In judging the response of the heart to changes in idioventricular pacing rates this phenomenon would have to be taken into account

The extent of the effect of atrial contraction is dependent on the heart rate as shown by the preceding results as well as by those of other investigators [19] This dependence presumably reflects the diminution in diastolic filling time at higher rates and the resulting increase in the importance of atrial contraction to ventricular filling

## Summary

Beat-to-beat variations of as much as 100 per cent in the external left ventricular stroke work have been found in 3 patients with acquired chronic complete heart block studied during idioventricular pacing These changes in work output reflect the presence or absence of a preceding

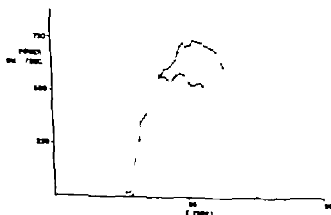


Fig 5 Instantaneous power output of the left ventricle in one subject during two ... beats at pacing rate of 60 beats per minute Zero time on the abscissa denotes the onset of the QRS deflection on the ECG The P R interval preceding one beat ( curve) was 0 15 sec that preceding the other (solid dot curve) was 0 48 sec

atrial contraction at [illegible] placement in time and the cardiac rate

[illegible]

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# The effect of quinidine on electrical energy required for ventricular defibrillation

*Donald J. Woolfolk, M.D.**
*William R. Chaffee, M.D.*
*Willard Cohen, M.D.*
*John F. Neville, M.D.*
*J. A. Abildskov, M.D.***
*Syracuse, N. Y.*

The use of brief, high voltage direct current pulses has been a significant advance in the therapy of cardiac arrhythmias.[1] The rapidity and relative certainty with which some arrhythmias can be terminated by this means also facilitates evaluation of factors involved in the conversion of arrhythmias. In the present study, the effect of quinidine on the electrical energy required for ventricular defibrillation has been investigated. Previous studies of the effect of quinidine on the ease with which defibrillation can be accomplished have given conflicting results.[2-4]

## Materials and methods

Experiments were performed on 20 dogs in the weight range of 10 to 18 kilograms. The animals were anesthetized with sodium pentobarbital, 25 mg. per kilogram, and sodium barbital, 400 mg. per kilogram. The latter long-acting agent was used to provide a uniform level of anesthesia throughout each experiment and minimize possible effects of this level on the energy necessary for defibrillation. Tracheotomy was performed and the animals were artificially hyperventilated with a mixture of 95 per cent oxygen and 5 per cent carbon dioxide. This had the object of fixing alveolar $CO_2$ at a level close to that in the inspired gas and maintaining stable $P_{CO_2}$ and pH, together with adequate oxygenation, thus minimizing the possible effect of these items on the energy requirements for defibrillation.

Ventricular fibrillation was induced by electrical stimulation at a rate of 40 c.p.s. using a bipolar needle electrode inserted into the myocardium through the intact chest wall. The onset of fibrillation was considered to be the moment of application of the stimulus, and a D.C. shock of the energy level being tested was applied after 6 seconds of fibrillation. If the test shock was unsuccessful, defibrillation was accomplished with a higher energy shock to permit continuation of the experiment.

From the Department of Medicine, [illegible] State University of New York, Upstate Medical Center, and the Veterans Administration Hospital, Syracuse, N. Y.
This investigation was supported by Research Grant HE-[illegible] from the National Heart Institute [illegible] and Veterans Administration Research Funds.
Received for publication Jan. 18, 1966.
*Post-Doctoral Heart Research Fellow, United States Public Health Service, Training Grant 5 T1 HE 5428.
**Address for correspondence: Department of Medicine, State University of New York, Upstate Medical Center, 750 East Adams St., Syracuse, N. Y. 13210.

A recovery period of at least 1 minute in normal sinus rhythm was allowed to elapse before ventricular fibrillation was reinduced. Three to five energy levels of D.C. shock were tested in each experiment and an effort was made to include one level which was usually successful, one which was usually unsuccessful, and an intermediate level. Each energy level was tested ten times with individual application of the various levels carried out in rotation. The time required for this evaluation of energy necessary for defibrillation under a given set of conditions depended on the number of energy levels tested and the number of failures which had to be followed by a second shock of higher energy level. To make the experiment as uniform as possible, each evaluation of energy requirements under new conditions was made at 1 hour intervals.

Direct current shocks were furnished by a capacitor discharge type of defibrillator through circular electrodes 8 cm. in diameter. The skin sites to which the electrodes were applied were prepared by shaving and the application of an abrasive conductive gel, and electrodes were bound to sites on the right and left lateral chest walls.

The spontaneous variability of energy required for defibrillation under the conditions of these experiments was evaluated in 6 experiments. Fibrillation was repeatedly induced and terminated over a 3 hour period, which was comparable to the time required in most of the experiments in which the effects of quinidine were evaluated. The effect of quinidine was studied in 11 experiments. One to three 200 mg. doses of quinidine gluconate were administered intravenously in these experiments, and a series of test shocks was applied beginning approximately 5 minutes after each dose.

Because of the known hypotensive effect of quinidine and the possible influence of blood pressure on energy required for defibrillation, femoral arterial pressure was recorded continuously in 3 experiments. After the administration of quinidine and the application of test shocks to define the energy required for defibrillation, angiotensin was infused with a variable-speed pump and the infusion rate was regulated to maintain monitored blood pressure at the level which existed prior to the administration of quinidine. In these 3 experiments a series of test shocks was then applied under the new condition.

### Results

There was variability in the energy required for defibrillation in different animals. This ranged from an occasional successful defibrillation with an energy level of 10 watt-seconds in one animal to a level of 30 watt-seconds for an even occasional defibrillation in another animal. Spontaneous variability of energy required for defibrillation was much less marked in the individual experiments in which this was investigated. An example of these results is shown in Fig. 1 and a summary of results in the 6 experiments in which spontaneous variability was observed is illustrated as part of Fig. 3. In the experiment illustrated in Fig. 1, ten applications of 20 watt-second shocks resulted in one successful defibrillation at the beginning of the experiment, two successful defibrillations 1 hour later, and one defibrillation after 2 hours. Similar small variability in the number of successful defibrillations at energy levels of 30 and 40 watt-seconds is also shown.

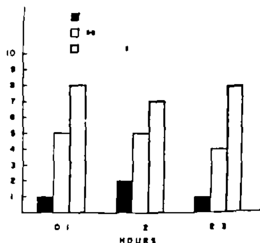



Fig. 1. Spontaneous variabilities of energy required for ventricular defibrillation in one experiment. The number of successful defibrillations achieved with 10 applications of shocks of the energy levels shown are indicated by the height of the bars.

Quinidine increased the electrical energy required for defibrillation. This is illustrated by the data from one experiment shown in Fig. 2 and by Fig. 3 which shows some of the data from all 11 experiments in which quinidine was administered. In the experiment the results of which are shown in Fig. 2, shocks of 30 watt-seconds resulted in successful defibrillation in 5 of 10 applications prior to the administration of quinidine. The observations made 1 hour later and beginning 5 minutes after the intravenous injection of 200 mg. of quinidine showed no successful defibrillation with shocks of that energy level. There were likewise no successful defibrillations at this energy level after the administration of an additional 200 mg. of quinidine. Shocks of 40 watt-seconds successfully defibrillated the ventricles in 6 of 10 applications prior to the administration of quinidine and were never successful after 200 and 400 mg. of quinidine had been given. Prior to the administration of quinidine, 50 watt-second shocks were uniformly successful in producing ventricular defibrillation. After 200 mg. of quinidine this energy level achieved defibrillation in 3 of 10 applications and was successful in only 2 of 10 applications after a total dose of 400 mg. of quinidine.

Fig. 3 shows results from 17 experiments. The number of successful defibrillations with an energy level which usually resulted in defibrillation prior to the administration of quinidine is plotted on the ordinate. This energy level is thus not the same for all experiments illustrated. Time is represented on the abscissa. The data represented by dotted lines are from experiments in which no quinidine was given and show the small spontaneous variability in energy necessary to accomplish defibrillation. The solid lines indicate the effect of quinidine on energy levels necessary to defibrillate the ventricles. With one exception, there were always fewer successful defibrillations with a given shock energy after the administration of quinidine, and larger doses of quinidine increased this effect.

In the 3 experiments in which blood pressure was monitored, there was a consistent fall followed by a gradual rise in

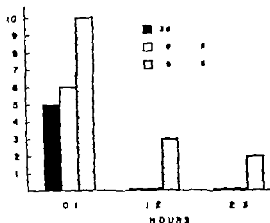


Fig. 2. Energy requirements for ventricular defibrillation before the administration of quinidine and after 200 mg. of quinidine 5 minutes before the observations shown for the 1-2 hour period and an additional 200 mg. before the 2-3 hour observation.

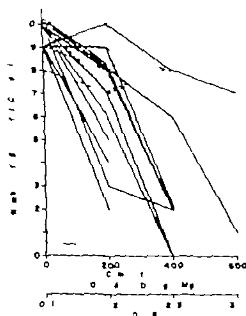


Fig. 3. Data from 17 experiments showing the number of successful ventricular defibrillations achieved with 10 applications of electric shock. Data represented by dotted lines are from experiments in which no quinidine was given and illustrate the small spontaneous variability of energy requirements for defibrillation under the conditions of these experiments. The solid lines show data from experiments in which quinidine was given in the amounts indicated and show the decreased number of successful conversions after this medication. The data shown represent different energy levels for the different experiments. An energy level which usually resulted in [illegible] defibrillations in the initial observations was chosen for this illustration.

pressure after the administration of either 200 or 400 mg. of quinidine. Five minutes after quinidine had been given the series of trial shocks was begun. At that time the blood pressure level was lower than the control by amounts ranging from 21 to 49 mm. Hg systolic and 31 to 48 mm. Hg diastolic. When angiotensin was infused and the blood pressure levels were restored to control values, the energy levels required for defibrillation were the same as those after quinidine alone. This suggests that the increased energy levels required for defibrillation after quinidine were the result of effects other than those on blood pressure.

## Discussion

In this study, quinidine increased the energy of D.C. shocks necessary to achieve ventricular defibrillation. Blood pressure levels were reduced by quinidine, but the increased energy levels required for defibrillation were not altered by the restoration of control blood pressure levels with angiotensin. Spontaneous variations in the energy necessary for ventricular defibrillation occurred but were slight compared to those which followed the administration of quinidine.

The energy levels required for ventricular defibrillation in this study were smaller than those which have been reported to be effective for this purpose.[4] The reason for *this difference is not certain, but the short* controlled duration of fibrillation and the measures employed to stabilize the anesthesia level, $PCO_2$, and blood pH in these experiments may be involved.

The mechanism by which quinidine increased the energy required for ventricular defibrillation is not apparent from these experiments. The cardiac actions of this drug include decreasing the excitability and increasing the refractory period. The most likely effect of electric shock in terminating fibrillation is that of exciting all or most of the cardiac tissue at one time. This leaves all or most of the heart in a refractory state and blocks propagation of the irregular activation fronts which are probably present in fibrillation. Whatever the basic nature of the disorder, decreased excitability after quinidine may reduce the mass of tissue which is activated and thus rendered inexcitable by electric shock. *Quinidine is known to increase* the threshold for the induction of fibrillation and this effect may also be the result of decreased excitability.[5] Lengthening of the refractory period may have a similar effect in that some cardiac elements which might have been excited by a given shock, had they been in a more advanced state of recovery, are not activated when their refractory period has been prolonged by quinidine.

Results of this study indicate that higher energy level shocks are necessary to terminate ventricular fibrillation after the administration of quinidine. This may be of some significance in the clinical use of electric shock for ventricular defibrillation in that some patients with this dysrhythmia may have previously received quinidine for the control of other arrhythmias. The results should not be taken to indicate a similar effect of quinidine in atrial fibrillation. Quinidine has a vagolytic action which reduces the degree of dispersion of atrial refractory periods.[7] If this effect existed alone, it might enhance the likelihood of terminating fibrillation, but it is complicated by the direct actions of quinidine on atrial muscle which include prolonging the refractory period and probably increasing the disparity of refractory periods. The design of this study of ventricular fibrillation and quinidine would *also be appropriate for the evaluation of* factors which influence the energy requirements for atrial defibrillation and the effect of factors other than quinidine in ventricular fibrillation.

## Summary

A technique for the evaluation of the electrical energy necessary for ventricular defibrillation under various controlled conditions was developed. Using this technique, quinidine was found to strikingly increase the energy necessary for defibrillation.

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# Observations on the effect of external counterpressure on the circulation through the forearm

*B. L. Ardill, B.Sc., M.B.*
*P. H. Fentem, M.Sc., M.B.*
*London, England*

The interpretation of measurements of blood flow in the forearm is complicated by the difficulty in separating the contribution of the skin circulation from that of the muscle circulation. Methods in current use for measuring blood flow in the skin and muscle compartments of the forearm are all subject to criticism.

Iontophoresis of adrenaline to abolish cutaneous blood flow[1] is effective only when a high concentration of adrenaline is achieved in the skin. It is impossible to ensure that some of this adrenaline does not diffuse into the underlying muscle or enter the blood stream in sufficient quantities to exert central effects.

Attempts to deduce changes in blood flow from changes in the oxygen saturation of the effluent venous blood of the two forearm tissues depend on the assumptions that oxygen consumption remains constant and that the ratio of blood flow through nutrient and non-nutrient channels is unchanged.

Methods in which changes in the thermal conductivity of the tissues[2,3] are used as an indication of changes in blood flow are at best only semiquantitative and, like techniques which depend on the rate of clearance of a diffusible ion[4] or radioactive gas[5] are open to criticism on the grounds that they measure the blood flow through a very small sample of the tissue which may not be representative of the whole and which may have been disturbed by mechanical trauma due to the insertion of the tracer or probe. Recently Hyman, Burnap and Lucas[6] using the segmental plethysmograph technique noted a decrease in the measured blood flow through the forearm as the counterpressure in the instrument was raised. In a subsequent paper Hyman and associates confirmed this finding using a capacitance plethysmograph with a pneumatic cuff inflated to various pressures mounted under the screens. They observed a progressive fall in measured blood flow as the counterpressure was raised from 5 to 25 mm Hg. With a further increase in counterpressure there was little change in blood flow until the counterpressure exceeded 35 mm Hg, when blood flow again declined with a further increase in counterpressure.

The flat portion in the curve between pressures of 25 and 35 mm Hg they took to represent a condition in which the skin capillaries were occluded because of the decrease in transmural pressure occasioned by the counterpressure, whereas the deeper

[illegible]
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muscle capillaries remained largely unaffected. Thus the recording of blood flow in the forearm with an appropriate counterpressure applied would give a measure of blood flow in muscular tissue only, whereas removal of counterpressure would allow the total blood flow in skin and muscle to be recorded in the usual manner.

In the light of the foregoing criticisms of other methods of separating blood flow in skin and muscle, the claim that by means of this maneuver it is possible to obliterate the circulation in the skin of the forearm without modifying the flow in muscle merits careful scrutiny.

This paper describes a series of experiments designed to test this hypothesis using a water filled plethysmograph suitably modified to enable various counterpressures to be applied to the forearm.

**Methods**

The subjects, with one exception (*see below*), were normal healthy men varying in age between 19 and 39 years. All measurements were taken with the subject in the supine position, and a rest period of 15 minutes was allowed to elapse before measurements were started.

Laboratory temperature varied in different experiments between 22° and 24 C but was held to within 1.5 C in any one experiment, with the exception of heating experiments.

*Blood flow in the forearm* was measured by venous occlusion plethysmography using temperature controlled water filled plethysmographs.[8] The temperature of the water in the plethysmographs was maintained at 34 ± 0.5 C. One instrument was modified as previously described by Wallace[17] to permit measurements of blood flow in the forearm at different counterpressures between 10 and 60 cm H O. Particular attention was paid to the fit between the forearm and the hard rubber end pieces of the plethysmograph in order to prevent bulging of the soft latex sleeve when the water pressure was raised.

*Effect of pressure on flow.* Twelve measurements of blood flow were taken in a period of 3 minutes at each of the following counterpressures in sequence: 10, 25, 40, 1, 37, 32, 10, 27.5, 50, 15, 55, 30, 10, 20, 4. The opposite forearm served as a control and was exposed to a counterpressure of 15 cm H O throughout. To exclude the effects of the circulation in the hand, cuffs were inflated at the wrists to a pressure of 200 mm Hg one minute before measurements were begun.[11]

A period of 1 minute was allowed to elapse after the counterpressure was applied before any measurements were taken; this was to allow equilibration of pressure throughout the tissues of the forearm. At every third change of counterpressure the wrist cuffs were released for 4 minutes and then the cycle was repeated.

*Heating.* The subjects were heated by means of a cradle carrying six 1 0 watt tungsten filament bulbs located over the trunk. Oral temperature was recorded before and during the period of heating, which was continued until the temperature had risen by about 0. °C.

Groups of eight measurements of blood flow were made at each of two counterpressures, 10 and 45 cm H O, in the experimental forearm before and every 15 to 20 minutes during heating. The lower counterpressure was chosen as that least likely to affect the circulation through the skin of the forearm. The higher pressure was chosen in the light of the results of Hyman and associates[4] as the pressure most likely to occlude the circulation through the skin of the forearm in all subjects, although we recognized that this pressure may also cause a diminution in the forearm muscle blood flow in some subjects.

*Exercise.* The experimental forearm was exercised by having the subject rhythmically squeeze with his hand a water filled rubber bulb attached to a modified 0 ml record syringe approximately 0 times in 2 minutes. Squeezing the bulb raised the plunger of the syringe, which was weighted with a 2 kilogram weight. This degree of exercise was sufficient to fatigue the forearm muscles within the 2 minute period.

Eight measurements of blood flow in the forearm were taken at counterpressures of 10 and 4 cm H O before exercise in order to determine the resting flow. Immediately after the period of exercise, 6 measurements of blood flow were made at a counterpressure of 45 cm H O, followed by 6 measurements at a counterpressure of

10 cm $H_2O$. This pattern was then repeated until blood flow had almost returned to resting level.

The control forearm was exposed to a counterpressure of 1 cm $H_2O$ throughout the period of exercise.

*Skin reactive hyperaemia.* Light measurements of blood flow were made in the experimental forearm and then the pressure in the plethysmograph was raised to 4 cm $H_2O$ and maintained at that pressure for 4 minutes. The pressure in the plethysmograph was then quickly dropped to 10 cm $H_2O$ and blood flow was recorded for the next 3 minutes. The opposite forearm served as a control being exposed to 1 cm $H_2O$ throughout the experiment.

**Results**

*Effect of increased counterpressure.* The effect on blood flow in the forearm of 6 subjects of counterpressures between 10 and 50 cm $H_2O$ is shown in the Appendix. Each figure is the mean of twelve measurements of flow, and the standard deviation is also included. The corresponding mean blood flow in the opposite control forearm is also given, together with the standard deviation.

The results in all 6 cases show a decline in blood flow with increasing counterpressure (See Fig. 1). In only 2 subjects (N.T.L. and B.L.A.) is there any evidence for a flat portion in the curve. However when variations in flow in the control fore-

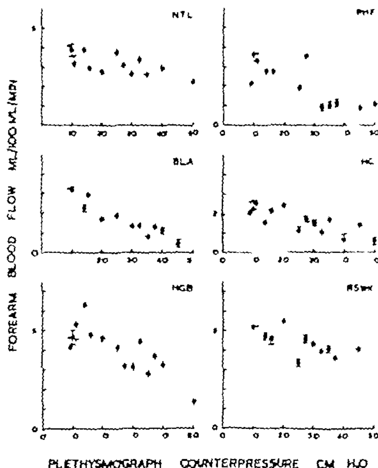



Fig. 1. The effect of counterpressure in the plethysmograph on forearm blood flow in 6 subjects. Mean of 3 (in the case of N.T.L. 8) individual measurements ± 1 standard deviation.

trin ue taken into account the significance of this becomes doubtful

*Heating* The results of the 5 heating experiments are shown in Table I Mean values for blood flow as measured at counterpressures of 10 and 45 cm $H_2O$ both before heating commenced and at the end of the period of heating are tabulated together with the calculated difference in flow at the two counterpressures

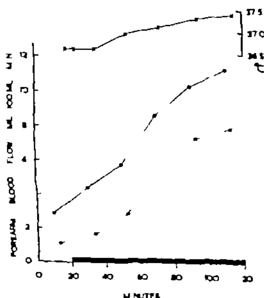



Fig Effect of body heating 0 9 kilowatt on forearm blood flow in a normal subject Each point is the mean of 8 individual flow measurements *Open dot curve* Forearm blood flow with counter pressure of 10 cm $H_2O$ in plethysmograph *Solid dot curve* Forearm flow with counterpressure of 45 cm $H_2O$ X curve Oral temperature

In all cases heating caused a rise of at least 100 per cent in total blood flow in the forearm However in only one individual was the increase in flow in tissues affected by a counterpressure of 45 cm $H_2O$ greater than that in tissues unaffected by this counterpressure

Fig 2 shows the results obtained in one experiment (P H F ) Here total blood flow was raised from 2 9 to 11 2 ml per 100 ml per minute in the experimental forearm during the period of heating Exposure to a counterpressure of 45 cm $H_2O$ lowered flow from 2 9 to 1 1 ml per 100 ml per minute before heating and from 11 2 to 7 8 ml per 100 ml per minute after heating Results during the course of heating show comparable decreases when counterpressure was applied

One of the subjects R was a patient who because of his height of 1 96 meters and weight of 50 8 kilograms had difficulty in maintaining his body temperature and during cold weather suffered from periods of hypothermia He was chosen because the ratio of skin to muscle in the forearm would be higher than average and it was assumed that the contribution of the skin component to total flow in the forearm would be correspondingly greater

The response of the forearm circulation to body heating in this case is shown in Fig 3 It will be noted that the rise in total flow in the forearm in response to an increase of 1°C in oral temperature was modest but the blood flow recorded in tissues unaffected by a counterpressure of

*Table I The effect of body heating on blood flow in the forearm**

| | Counterpressure (cm $H_2O$) | Subject | | | | |
|---|---|---|---|---|---|---|
| | | *B L A* | *P H F* | *R* | *C S* | *H I M* |
| Before heating | 10 | 5 1 | 2 9 | 1 3 | 2 3 | 4 5 |
| | 45 | 2 6 | 1 1 | 0 6 | 0 5 | ? 1 |
| | Difference | 5 | 1 8 | 0 | 1 8 | ? 4 |
| After heating | 10 | 12 0 | 11 | 4 0 | 10 4 | 1 0 |
| | 45 | 9 0 | 7 8 | 1 | 5 ? | 7 9 |
| | Difference | 3 0 | 3 4 | 1 9 | 2 | 4 1 |

* [illegible] pressures of 10 and 45 [illegible] $H_2O$ together with the [illegible] flow [illegible] counterpressures of 10 and 45 cm $H_2O$ Figures before heat [illegible] of 8 flows Figures after heating [illegible]

4 in H O in r s 1 w s fashion similar to that in the th r ubj t

*Ex rci e* Th p ttern f I lood flow re corded in th post x rcise period w s sim ilar in all f 5 xperiments on 4 subject Fig 4 show th results obtained in the 4

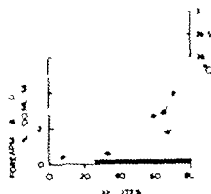



Fig 3 Bl r ff F h t 0 ) L I tt f r r bl x 1 Bl il t R I h p t th n f B n l lu l fl w m rcn t *Open d t* rve f r r Il d flo w th t rg ure t 10 m H2O n pl th m g r pl S *lid d t* ar f r rm fl w th t rp re ure ( 45 n H2O X w re O r ti nper t r

subject A repeat experiment on E H I gave a similar result. It will be seen that the flow through tissues affected by coun terpressure varied during the postexercise period and at times accounted for up to 0 per cent of the total blood flow in the forearm. Blood flow in the control forearm w s unchanged by the exercise.

*Cutaneous reactive hyperemia* Fig re cord the pattern of blood flow in the ex perimental and control forearms of 4 sub ject in the period immediately after the reduction in counterpressure on the experi mental forearm to 10 cm H O after ex posure to a counterpressure of 45 cm H O for 4 minutes. It will be seen that reactive hyperemia w s of an exceedingly small order.

## Discussion

Of the two method of application of counterpressure to the forearm segment namely immersion of the forearm in water and the inflation of a pneumatic cuff on the forearm the former might be expected to exert a more uniform pressure along the vertical diameter of the forearm since the

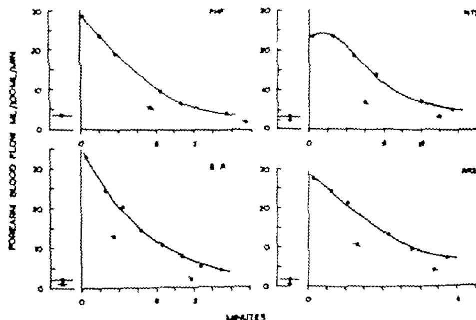



Fig 4 Measurement f fore rm blood flow t count rpre ures of 10 nd 45 cm H2O f fore and after a 2 minute period of rhythmic exercise of the forearm muscle Each point the m n of 6 individu l flow measurement *Open dot curve* Counterpres ure of 10 cm H O *Solid dot curve* Counterpre ur of 45 cm H2O

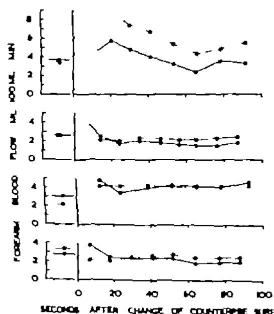



Fig 5 Pattern of forearm blood flow in experimental and control forearms after exposure of experimental forearm to counterpressure of 45 cm $H_2O$ for 45 minutes in 4 subjects *Solid dot curve* Experimental forearm at counterpressure of 10 cm $H_2O$ *Open dot curve* Control forearm at counterpressure of 15 cm $H_2O$ The points to the left of the vertical line marking the end of the period of exposure to counterpressure are the means of 8 flow measurements in the two forearms during the 2 minute period prior to exposure of the experimental forearm to counterpressure

pecific gravities of the forearm tissues and blood do not differ greatly from unity Thus we consider that with our technique the change in transmural pressure is likely to be approximately uniform over the cross section of the forearm provided that there is no interference with the transmission of pressure within the forearm tissues

Hyman and associates[4] suggest that a critical value of counterpressure must be exceeded before the pressure is transmitted to the deeper muscular tissues of the forearm thus implying a barrier to transmission of pressure in the subcutaneous region of the forearm Such a barrier would appear to be unlikely on anatomic grounds because the antebrachial fascia and intermuscular septae are not structurally arranged to resist externally applied pressure Furthermore if this situation were to exist in the upper arm also it would lead to the arterial pressure being overestimated by between 25 and 35 mm Hg when measured by the auscultatory method

The width of the pneumatic cuff is known to be of importance when measuring arterial blood pressure In particular narrow cuffs tend to lead to overestimation of arterial pressure[1] This is assumed to be due to the peculiarity of the pressure profile below the cuff which has been shown to be wedge shaped[12]

In our experiments the length exposed to counterpressure was 1 cm whereas Hyman and associates[4] used a cuff 6 5 cm in width Decreasing the length exposed to pressure would tend to decrease the volume of deep tissue experiencing increased pressure Thomson and Doupe[13] recorded a maximal tissue pressure of 89 per cent of the applied cuff pressure 3 cm in from the edge of the cuff at a depth of 3 cm in the forearm At the same depth they did not achieve a reading of 100 per cent until the needle was more than 5 cm in from the edge of the cuff They demonstrated a similar effect at depths less than 3 cm

The results of Craf and Rowell[14] support this hypothesis They recorded a greater fall in forearm blood flow with increasing counterpressures in the range of 10 to 20 cm $H_2O$ when they used two 5-cm segmental plethysmographs side by side on the forearm than with a single 5 cm plethysmograph We would suggest therefore that the length of forearm segment exposed to counterpressure may well be critical

One further criticism of the rationale of the technique is its implied assumption of a uniform pressure in small vessels in the forearm With vasomotion the pressure in individual capillaries will be constantly changing and although the mean capillary pressure in a given volume of tissue may not alter under resting conditions there may well be a wide scatter of pressures around this mean value Indeed the range recorded by Landis in 12 measurements of pressure at the arteriolar end of human capillaries was from 21 to 48 mm Hg giving a mean of 32 mm Hg the figure quoted by Hyman Thus even if the counterpressure is applied evenly to the skin it is unlikely that a pressure sufficient

to close skin capillaries in which the pressure is above the mean will not affect those deeper muscle capillaries in which the pressure is below the mean.

It has already been shown by Lewis and Haynal and Landis that when a vascular bed undergoes vasodilatation, the mean pressure in the capillaries rises. Landis recorded pressures of 32, 24, and 40 mm Hg at the arteriolar end of capillaries under resting conditions in 3 subjects. After heating, the corresponding values were 68, 72, and 62 mm Hg. Thus even if the condition outlined above are fulfilled in the resting state, one cannot assume that the same counterpressure will exert a similar effect on skin capillaries when the blood flow is altered. In effect, if the Hyman hypothesis holds true, the condition is one of critical closure of skin vessels, and the wide variation in flow cessation pressure with alteration in vasomotor tone is well documented.[12, 8]

When compiling our results we were impressed by the scatter of individual flow measurements at each level of counterpressure. Inspection of the Appendix will indicate the degree of confidence with may be attached to any one flow measurement when drawing a curve relating apparent flow to counterpressure.

Halperin and associates,[4] Wallace,[5] using a water-filled plethysmograph, Hyman and associates,[7] and Graf and Rowell[13] using the segmental plethysmograph have investigated the effect of increased counterpressure on blood flow in the forearm. Our results confirm their findings of a decrease in apparent flow with increase in pressure above 10 cm $H_2O$ and the slope of the curves relating flow to counterpressure is similar (See Fig. 6.)

The curves of Burton and Yamada[17] and Ashton[8] are plotted to show the relationship between forearm blood flow and transmural arterial pressure and cannot therefore be compared directly with our results. However, the scatter of individual flow measurements at a given pressure in Burton and Yamada's paper is similar to our own.

Since we were unable to demonstrate the flat portion in the curve described by Hyman and associates, the inability of our method to achieve satisfactory separation of forearm blood flow into its two components was not surprising. The explanation of this must lie in the fact that the results described here were obtained with a 15-cm long water-filled plethysmograph rather than with the shorter 6.5-cm instrument.

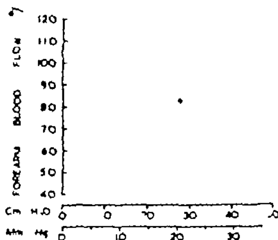



Fig. 6. Effect of counterpressure on forearm blood flow. *Solid dots*: Mean of results in 6 subjects. (For each subject the mean flow at different counterpressures was expressed as a percentage of mean flow at counterpressure of 10 cm $H_2O$.) *Open dots*: Mean results of Hyman and associates in 6 subjects using segmental plethysmograph expressed as a percentage of flow at 10 mm Hg. *Open squares*: Results of Halperin and associates in 6 subjects using a water-filled plethysmograph, expressed as a percentage of flow at 6.5 cm $H_2O$. X: Results of Graf and Rowell[13] in 17 experiments in 9 subjects using segmental plethysmograph 5 cm wide [illegible] on the forearm expressed as percentage of flow at 10 cm $H_2O$.

The application of counterpressure to a 6-cm segment does appear to achieve satisfactory separation of blood flow, but it will be important to know what length of segment is critical and to what extent results are influenced by such factors as diameter of the forearm and thickness of the skin.

Inspection of Table I shows that with one exception, the estimate of muscle blood flow (measurement at a counterpressure of 45 cm $H_2O$) in every case showed a greater increase with heating than did the estimate of skin blood flow (difference between measurements at 10 and 45 cm $H_2O$). These surprising results would, if the hypothesis

is correct imply that the conclusion supported by work using four different techniques that the increase in forearm blood flow during body heating is confined to the skin" is wrong

The technique which we used to record postexercise hyperemia differed slightly from that used by Hyman and associates[8] In our experiments we recorded alternately at counterpressures of 10 and 45 cm $H_2O$ during the period of hyperemia following exercise It might be argued that the rapid changes in counterpressure with almost immediate recording of blood flow would not allow sufficient time for equilibration to occur in the forearm circulation However the experiments of Halperin and associates[1] support our own finding that blood flow is stable after the equilibration of forearm volume at a new level—a process which is almost complete within 10 seconds of the change in counterpressure

The results of the exercise experiments show that flow through tissues affected by counterpressure (presumed to be skin flow) was relatively high during the postexercise period at times exceeding 30 per cent of the total forearm blood flow Furthermore this fraction varied considerably within the period of study

Blood flow through skin overlying muscles which have been exercised may however rise during the postexercise period as is suggested by the recent work of Robin on and associates[3] *on the calf* They recorded a rise in the temperature of the skin of the calf and in the temperature of blood draining the skin of the calf during the post exercise period Thus they interpreted as indicating an increase in blood flow in the skin during this period

The mechanism of this inferred increase in blood flow in the skin has not been investigated If however the increase is due to a direct heating effect of the underlying muscle mass one might expect the use of water filled plethysmographs with a large heat capacity held at a constant temperature to minimize the effect

In view of the variability and extent of the changes in postexercise flow in the forearm caused by counterpressure in the water filled plethysmograph we conclude that with this apparatus the method does not provide a reliable means of separating blood flow through muscle from that through skin under conditions of raised blood flow in muscle

That reactive hyperemia occurs in the skin of the forearm is easily demonstrated by observing the changes in the temperature and color of the skin after a period of arrest of the circulation to the part If exposure to counterpressures above 35 mm Hg causes arrest of the circulation in the skin it is reasonable to assume that exposure to 45 cm $H_2O$ counterpressure for a period of 45 minutes would result in some evidence of hyperemia

The results of 4 experiments all show that the first flow after removal of counterpressure was elevated but the rise was in all cases very small For comparison Patel and Burton[2] recorded an initial flow of 65 ml per 100 ml per minute in the finger which can be regarded as representing mainly flow in skin after a period of arterial occlusion that lasted 7 minutes This would imply that during the period of exposure to counterpressure the tissues of the forearm were experiencing a flow of blood adequate for their metabolic needs Our finding is in keeping with the results of Dornhorst and Whelan[28] who used a counter pressure of 67 cm $H_2O$ for much shorter periods

It would appear therefore that although the application of counterpressure does lower the forearm flow and although the vessels situated near the surface of the forearm are more likely than deeper vessels to be affected by counterpressure factors other than site also influence the susceptibility of blood vessels to counterpressure It is likely that a reduction in flow occurs preferentially in vessels which are already in a relative state of constriction Furthermore the degree of localization of the effects of counterpressure to superficial tissues will be influenced by the length and diameter of the segment exposed to counterpressure

We conclude that the selection of a suitable segment length for the counterpressure technique puts a serious limitation on its general use and that the application of counterpressure in the conventional water filled plethysmograph does not provide a reliable method for distinguishing between the contribution of the muscle

Table II Appendix

| Subject | | Counterpressure (cm H₂O) | | | | | |
|---|---|---|---|---|---|---|---|
| | | 10 | 15 | 20 | 25 | 35 | 50 |
| BEA | Experimental | | | | | | |
| | Mean | 4 16 | 3 | [illegible] | 91 | [illegible] | 1 71 |
| | SD | 0 [illegible] | 0 41 | 0 [illegible] | 0 [illegible] | 0 20 | 0 40 |
| | Control | | | | | | |
| | Mean | [illegible] 91 | [illegible] | 3 40 | 4 45 | [illegible] | [illegible] 6 |
| | SD | 0 [illegible] | 0 46 | 0 [illegible] | 0 [illegible] | 0 31 | 0 [illegible] |
| EHH | Experimental | | | | | | |
| | Mean | [illegible] | [illegible] | [illegible] | 8 | 1 | 05 |
| | SD | 0 [illegible] | 0 [illegible] | 0 33 | 0 57 | 0 36 | 0 [illegible] |
| | Control | | | | | | |
| | Mean | 3 | [illegible] 58 | [illegible] 8 | [illegible] | [illegible] 81 | [illegible] |
| | SD | 0 [illegible] | 0 [illegible] | 0 [illegible] | 0 35 | 0 5 | 0 11 |
| NEE | Experimental | | | | | | |
| | Mean | 4 [illegible] | [illegible] | [illegible] 15 | [illegible] | 2 99 | [illegible] |
| | SD | 0 [illegible] | 0 [illegible] | 0 [illegible] | 0 35 | 0 44 | 0 41 |
| | Control | | | | | | |
| | Mean | [illegible] | [illegible] | [illegible] | 4 [illegible] | [illegible] 71 | [illegible] |
| | SD | 0 [illegible] | 0 41 | 0 [illegible] | 0 [illegible] | 0 [illegible] | 0 [illegible] |
| HCB | Experimental | | | | | | |
| | Mean | 4 2[illegible] | 4 [illegible] | [illegible] 11 | [illegible] | 4 [illegible] | 4 [illegible] |
| | SD | 0 4[illegible] | 0 31 | 0 [illegible] | 0 [illegible] | 0 [illegible] | 0 3 |
| | Control | | | | | | |
| | Mean | 3 [illegible] | [illegible] | 4 [illegible] | [illegible] | 4 [illegible] | 4 0[illegible] |
| | SD | 0 [illegible] | 0 [illegible] | 0 [illegible] | 0 [illegible] | 0 [illegible] | 0 [illegible] |
| RSWK | Experimental | | | | | | |
| | Mean | 3 61 | [illegible] | 4 81 | 4 7[illegible] | 4 [illegible] | 5 50 |
| | SD | 0 18 | 0 27 | 0 [illegible] | 0 [illegible] | 0 31 | 0 [illegible] |
| | Control | | | | | | |
| | Mean | 4 [illegible] | 5 7 | 4 [illegible] | [illegible] 9 | 4 [illegible] | 4 [illegible] |
| | SD | 0 [illegible] | 0 [illegible] | 0 41 | 0 [illegible] | 0 [illegible] | 0 [illegible] |
| HC | Experimental | | | | | | |
| | Mean | 05 | [illegible] 26 | 5 | 1 [illegible] | 2 15 | 45 |
| | SD | 0 31 | 0 [illegible] | 0 90 | 0 45 | 0 28 | 0 [illegible] |
| | Control | | | | | | |
| | Mean | [illegible] | 3 15 | 3 19 | 3 14 | 3 [illegible] | 3 20 |
| | SD | 0 [illegible] | 0 [illegible] | 0 [illegible] | 0 50 | 0 2[illegible] | 0 [illegible] |

M [illegible]

and skin circulations to total blood flow in the forearm


## Summary

The effect of exposure of a 15 cm forearm segment to counterpressures in the range of 10 to 50 cm $H_2O$ on forearm blood flow was measured in each of 6 subjects. An increase in counterpressure resulted in an approximately linear decrease in forearm blood flow. There was no consistent evidence for the existence of a range of counterpressure over which apparent blood flow remained constant.

Results of experiments in which forearm blood flow was measured at counterpressures of 10 and 45 cm $H_2O$ during body heating and during the period of elevated

*experimental arm (cm $H_2O$)*

| 25 | 27.5 | 30 | 32.5 | 35 | 37.5 | 40 | 45 | 50 |
|---|---|---|---|---|---|---|---|---|
| 1.94 | 1.58 | 1.39 | 1.39 | 0.84 | 1.32 | 1.16 | 0.45 | 0.66 |
| 0.39 | 0.47 | 0.47 | 0.34 | 0.32 | 0.32 | 0.16 | 0.19 | 0.29 |
| 4.85 | 3.87 | 4.06 | 4.86 | 3.87 | 5.14 | 6.37 | 3.83 | 4.18 |
| 0.22 | 0.39 | 0.32 | 0.34 | 0.34 | 0.35 | 0.57 | 0.17 | 0.84 |
| 1.99 | 3.51 | 1.23 | 0.99 | 1.03 | 1.15 | 0.99 | 0.96 | 1.13 |
| 0.44 | 0.54 | 0.22 | 0.12 | 0.19 | 0.25 | 0.31 | 0.30 | 0.79 |
| 3.50 | 4.61 | 4.09 | 3.54 | 4.30 | 3.48 | 3.36 | 4.63 | 5.91 |
| 0.10 | 0.51 | 0.15 | 0.28 | 0.50 | 0.38 | 0.35 | 0.44 | 1.07 |
| 3.78 | 3.08 | 2.62 | 3.38 | 2.63 | 3.03 | 2.94 | 2.10 | 21 |
| 0.37 | 0.31 | 0.35 | 0.60 | 0.24 | 0.25 | 0.3 | 0.21 | 0.34 |
| 4.09 | 3.85 | 3.77 | 4.52 | 3.82 | 4.65 | 4.08 | 4.08 | 3.95 |
| 0.25 | 0.78 | 0.4 | 0.19 | 0.39 | 0.18 | 0.45 | 0.50 | 0.41 |
| 4.14 | 3.17 | 3.14 | 4.44 | 2.78 | 3.71 | 3.24 | — | 1.55 |
| 0.31 | 0.32 | 0.39 | 0.68 | 0.33 | 0.49 | 0.40 | — | 0.34 |
| 4.83 | 4.09 | 3.91 | 5.95 | 4.04 | 5.77 | 4.49 | — | 4.01 |
| 0.62 | 0.47 | 0.32 | 0.83 | 0.29 | 0.33 | 0.46 | — | 0.56 |
| 3.35 | 4.65 | 4.33 | 3.94 | 4.10 | 3.63 | 2.20 | 4.10 | 3.26 |
| 0.16 | 0.15 | 0.44 | 0.30 | 0.19 | 0.21 | 0.30 | 0.37 | 0.15 |
| 5.58 | 5.68 | 4.91 | 5.71 | 4.83 | 5.86 | 6.41 | 4.58 | 5.48 |
| 0.11 | 0.16 | 0.18 | 0.24 | 0.24 | 0.27 | 0.67 | 0.28 | 0.4 |
| 1.13 | 1.6 | 1.53 | 1.06 | 1.71 | 0.93 | 0.69 | 1.43 | 0.63 |
| 0.2 | 0.20 | 0.13 | 0.36 | 0.35 | 0.41 | 0.74 | 0.29 | 0.18 |
| 8 | 3.17 | 3.0 | 2.98 | 3.54 | 3.42 | 2.95 | 2.9 | 3.70 |
| 0.27 | 0.36 | 0.27 | 0.83 | 0.42 | 0.52 | 0.42 | 0.31 | 0.57 |

blood flow in the forearm after exercise of the forearm muscles did not demonstrate that exposure to a counterpressure of 45 cm $H_2O$ in our apparatus caused suppression of blood flow through the skin of the forearm

Exposure of the forearm segment to a counterpressure of 45 cm $H_2O$ for 45 minutes did not result in reactive hyperaemia comparable to that induced in skin at other sites by period of arterial occlusion of much shorter duration

Although it may be possible to suppress blood flow in skin without affecting blood flow in muscle by applying counterpressure to a short segment of forearm our experiments indicate that it is not possible to do this in longer segments

## Appendix

Table II present forearm blood flows (mean and standard deviation) for experimental forearm exposed to different counterpressures as shown and for control forearm exposed to a counterpressure of 15 cm $H_2O$ throughout for each of 6 subjects. Figure for S.L.I. are the mean of 8 individual flows for all other subject the figures are the mean of 12 individual flows.

W h t th nk Fr fs A.D.M. Greenfi ll f r h upport nd n ur gement during th w rk Dr I C B n ter for perm s n t m estt t w t h p tient n l Mr D I I n f r t h n l tan

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# Endomyocardial biopsy

## Experimental study with a catheter technique

James R Wennemark M D *
Herbert M Sommers M D
Ralph S Zitnik M D **
Chicago Ill

Biopsy of the heart as an aid to diagnosis in endocardial and myocardial disease has been accomplished by various methods[1-3] Some techniques require a thoracotomy which limits their application Percutaneous methods have also been used but the hazard of cardiac tamponade or pulmonary complications during ventricular puncture is always present[4]

Biopsy of the myocardium by means of an intravascular catheter technique would have obvious advantages Multiple specimens could be obtained without the necessity of general anesthesia or thoracotomy Cardiac tamponade or pulmonary complications would not be a problem In 1962 Sakakibara and Konno introduced a bioptome or biopsy catheter and subsequently reported its successful use in animals and human beings[7,8] More recently Bulloch and associates[9] have suggested another catheter biopsy technique for obtaining specimens of the ventricular septum from the right ventricle

The present study was performed in dogs to determine the practicability and safety of the Konno intravascular biopsy catheter and the capability of this instrument to provide adequate samples for histologic and other studies

## Methods

Nineteen medium sized mongrel dogs were anesthetized with intravenous pentobarbital 15 to 30 mg per kilogram A standard 12 lead electrocardiogram (ECG) was obtained at the beginning and end of each procedure The right femoral artery was cannulated and pressures were obtained using a Statham P23 V strain gauge manometer Lead II of the ECG and the femoral arterial pressure were monitored throughout the procedure

The right jugular vein and right carotid artery were exposed surgically The bioptome was first inserted into the right jugular vein and advanced into the right ventricle where in 18 dogs two separate biopsy specimens were obtained and where in 1 dog only one specimen was obtained In 12 dogs the bioptome was then inserted into the right carotid artery and advanced into the left ventricle where one biopsy specimen was obtained All catheter manipulations were done under fluoroscopic control

From the Department [illegible] of Medicine [illegible] Northwestern University School of Medicine Chicago Ill
This work was supported by United States Public Health Service Research Grant [illegible]
Received for publication Jan 2 [illegible]
[illegible]

After the initial four experiments, the biopsy catheter was modified by adding a length of polyethylene No. [illegible]0 tubing along the side of the instrument. This was used to monitor blood pressure at the tip of the catheter and served as a constant check on the position of the bioptome.

On removal of the bioptome from the animal, the specimen was carefully taken from the instrument, gently blotted, and unfolded. The endocardial surface was placed on a portion of stiff paper or light cardboard so that distortion inherent in taking the biopsy would not become a permanent part of the fixed tissue. The specimen was oriented and arranged on the paper splint and then placed in cold formalin buffered to pH [illegible] with phosphate. All tissues were processed in the usual fashion and embedded in paraffin with sections cut at 5 microns. Sections were stained with hematoxylin and eosin, by the Heidenhain modification of the Mallory technique for connective tissue, and in some instances by the periodic acid-Schiff (PAS) technique with and without preceding alpha-amylase digestion. Elastic tissue stains were done using the Verhoeff technique with a Van Gieson counterstain.

Two dogs were sacrificed immediately after biopsy, 2 others 24 hours later, and 13 at time intervals varying from 12 to 21 days after biopsy. At the time of sacrifice the animals were again anesthetized with intravenous pentobarbital, and the ECG was repeated. The heart was quickly excised, weighed, and opened along the anterior wall of the inflow tract of the right ventricle and along the anterior wall of the outflow tract of the left ventricle in order to locate the biopsy site. Tissues were taken for histologic study from all identified biopsy sites as well as from all abnormal appearing areas. All tissue specimens from the heart were processed in a fashion similar to the biopsies.

## Results

Two animals developed complications. The coronary sinus was biopsied in one animal, resulting in fatal tamponade. In the second animal, the aortic valve was perforated, resulting in severe aortic insufficiency.

After modification of the catheter to include pressure monitoring, no serious complications were encountered. Frequent extrasystoles were observed during the actual biopsy procedure. No significant change in the systemic blood pressure was seen at the time of biopsy. ECG's taken immediately after the procedure and at the time the animals were sacrificed did not show any significant change. All animals surviving the initial procedure were alive and appeared to be healthy at the time of sacrifice.

Sections of the biopsy specimens usually revealed a portion of myocardium, and with careful embedding, the endocardial surface could be identified. Multiple sections producing a minimum of 10 to 15 slides could be cut from a single biopsy specimen. Hematoxylin and eosin stains proved to be best for the study of fine cellular detail (Fig. 1). Stains for connective tissue and elastic tissue were also contributory. Cellular morphology was well preserved, although there was a tendency for the fibers near the edges of the biopsy material to separate and spread apart because of the lack of supporting connective tissue (Fig. 2). In many instances, prominent contraction bands were present in myocardial fibers, particularly those oriented near the edges of the biopsy specimen (Fig. 3). Although no precautions were taken to minimize the dissolving of glycogen within the fibers, and no stains performed with the specific end of identifying that substance, moderate amounts of it were observed in specimens stained by the PAS technique. Purkinje fibers were identified in biopsy specimens from the left ventricle. Little difference could be seen between biopsy specimens from the right and left ventricle, with the possible exception that the endocardium was more easily identified in the specimens from the right ventricle.

Over half of the biopsy specimens taken from the right ventricle were obtained from the area near the junction of the anterior wall of the right ventricle with the interventricular septum. Usually, the biopsy site was located within that region which lies one half to two thirds of the distance between the base of the heart and the apex of the right ventricle. Biopsy scars in 3 dogs were found on the anterior



Fig. 1 Endomyocardial junction from right ventricular biopsy. The normal relationship between the endocardium and myocardium is shown in this section. The detail of the endocardium and myocardial fibers is good. Sections of this type can be obtained with careful handling of the biopsy specimen prior to fixation. Hematoxylin and eosin stain magnification X 130



Fig. 2 Myocardial fibers from an area near the edge of biopsy specimen. Fibers have separated [illegible] because of a natural tendency to spread apart from lack of supporting connective tissue. Prominent contraction bands are seen throughout these fibers. In this instance contraction bands are most likely related to the trauma of taking the biopsy specimen. Hematoxylin and eosin stain magnification X 350

medial wall of the right ventricle about midway between the tricuspid valve and the apex and in 4 dogs scars were identified on the posteromedial wall of the right ventricle within 1.5 cm from the tricuspid valve.

In the left ventricle the most common site of the biopsy was midway between the posterior and anterior papillary muscles in that region which lies approximately one half to two thirds of the distance between the mitral ring and apex of the left



Fig. 3 Cr... sect... n ... tmy... snb ... h... w... th... ... em... to... ... myocard... fiber ... and ... pillary bed. Fibers app... ... ... fiber ... ... ... Although the fiber are lightly ... ... Hematoxylin and eosin stain. magnification × 330.

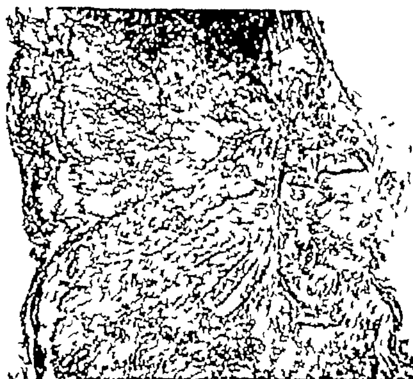


Fig. 4 Biopsy site in right ventricle 17 days after biopsy. The myocardial defect ... filled with organizing connective tissue and strand... of ... ... extending radially from the biopsy ... through the ... myocardial fibers. Hodgkin... Mallory ... stain, ... magnification × 53.

ventricle. In 3 dogs biopsy scars were present medial to the posterior papillary muscle near the interventricular septum, whereas only 1 dog had a scar at the apex of the left ventricle. In 1 dog the biopsy scar was found high on the lateral wall of the left ventricle just beneath the mitral valve.

Examination of 2 dogs sacrificed immediately after biopsy of the right ventricle showed small hemorrhagic areas with beginning mural thrombi at the biopsy site. Two dogs sacrificed 24 hours after biopsy showed a focal inflammatory process in the myocardium associated with interstitial hemorrhage, segmented neutrophils, and an overlying mural thrombus. By 12 days the defect showed a partially organized area with early collagen formation, and by 21 days the biopsy site had been replaced by a well formed scar (Fig. 4).

An unexpected finding in half of the dogs was the presence of an area of injury in the right atrium, usually on the muscular limbus that separated the inferior and superior venae cavae. The injury was manifested by a fibrous plaque or partially organized mural thrombus. In most hearts sections showed the thrombus to have occurred over an intact endocardial surface with no evidence of myocardial damage (Fig. 5), but in 1 dog sacrificed at 24 hours a marked inflammatory reaction extended through the entire wall and was associated with focal necrosis of myocardial fibers. In one instance a mural thrombus was present on the interior wall of the right atrium. The area of the limbus did not show any abnormalities. The dog with the largest mural thrombus in the right atrium also showed focal moderate to marked edematous changes in the tricuspid valve leaflets.

**Discussion**

The addition of a pressure monitoring channel to the biopsy catheter significantly improved the safety and ease of the procedure. Except for extrasystoles during the biopsy, no other complications at the



Fig. 5. Mural thrombus on wall of right atrium between the superior and inferior venae cavae 17 days after biopsy. The incompletely organized mural thrombus appears to involve only the surface of the endocardium. The endocardium is intact, although thickened beneath the thrombus. In most instances the thrombus was organized with only a fibrous plaque remaining over the endocardium at the time of sacrifice. The injury in the right atrium is considered to be due to the trauma of introducing the biopsy catheter. Heidenhain Mallory connective tissue stain; magnification X9.

time of the procedure were observed with the use of the modified catheter.

The bioptome itself is stiff, and manipulation within the vascular system, especially around curves, is therefore difficult. This characteristic of the catheter undoubtedly accounts for the damage to the right atrium that was observed.

The construction of the catheter makes thorough cleaning of it difficult if not impossible.

The cutting tip of the bioptome is oval in shape. The catheter can be advanced and a bite taken in ventricular tissue, but actual excision of the tissue is accomplished by crushing the myocardium between the jaws of the bioptome and withdrawal of the catheter with subsequent tearing of tissue rather than the making of a clean incision. The artifact induced by the crushing action of the bioptome can be minimized by the careful handling of the tissue before fixation, but frayed fibers, contraction bands, and other changes remain as a consequence of the method of taking the specimen.

The location of the biopsy sites and the speed of healing would indicate that the procedure would not under ordinary circumstances inflict a significant injury on the myocardium. The presence of the endocardial lesions in the right atrium would suggest that endocardial injury to sites other than that of biopsy can occur if the bioptome is used in its present form, although it is possible that the likelihood of such injury would be less in man than in the dog.

A small sample of endomyocardial fragments of the right or left ventricle cannot be expected to give the same amount of information as may be gained from percutaneous biopsies of visceral organs. Diseases of the endomyocardium frequently leave a residue of nonspecific fibrotic tissue which aids little in establishing the precise nature of the pathologic process.[1] Conversely, the diagnosis of such conditions as glycogen storage disease, endocardial fibroelastosis, and amyloid disease might be considerably aided by endomyocardial biopsy. The role of myocardial biopsy in obtaining tissue for serial biochemical and electron microscopic studies remains to be determined.

## Conclusions

Biopsy of the endomyocardium has been experimentally evaluated in the dog, using a biopsy catheter. The addition of a pressure monitoring channel to the catheter increased the safety of the procedure. An adequate amount of tissue was obtained for histologic and multiple histochemical studies, and these may be of considerable help in determining the nature of some obscure cardiac diseases. Some endocardial injury to sites other than those biopsied was observed in the right atrium. This was most likely due to the design of the biopsy catheter used in this study, which makes intravascular manipulation difficult.

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# Case reports

## Acceleration of the sinoatrial rate leading to complete heart block, an unusual mechanism for the Adams-Stokes syndrome

*Paul L. McHenry, M.D.**
*Suzanne B. Knoebel, M.D.*
*Indianapolis, Ind.*

The clinical picture associated with the Adams-Stokes syndrome when normal sinus rhythm prevails during symptom-free periods is in many ways distinct. Individuals with this phenomenon have been observed to have a very unstable functioning of the atrioventricular (A-V) conduction system manifested by abrupt and transient episodes of complete heart block and ventricular asystole, but some have also been free of Adams-Stokes attacks for long intervals of time.[1] The cardiac arrhythmias responsible for the syncopal episodes may be missed because of a rapid return to normal sinus rhythm. The pathophysiology underlying such examples of unpredictable and episodic heart block as have been reported heretofore is uncertain, but A-V block as a result of increased vagal tone has been implicated in a number of cases.[1-4]

The present report concerns a case in which acceleration of the sinoatrial (S-A) rate was documented as an unusual mechanism giving rise to complete heart block and ventricular asystole. Although an increase in atrial rate has been postulated as a possible cause of intermittent complete A-V block and Adams-Stokes attacks, such a mechanism has not, to our knowledge, been demonstrated clinically in man. The clinical course of this patient is otherwise quite typical of those individuals with the Adams-Stokes syndrome in whom normal sinus rhythm predominates between syncopal episodes. Some of the difficulties which may arise in the diagnosis and management of such cases are demonstrated.

### Case report

The patient, [illegible] 47-year-old woman, was admitted for the first time to the Indiana University Medical Center on Aug. 3, 1964, with the chief complaint of repeated blackout spells since February, 1964. Previous to the onset of the episodes she had been hospitalized briefly at her local hospital in May, 1964. At that time the chest [illegible] film, ECG, and routine laboratory studies were found to be normal, and she was discharged without diagnosis, although a psychophysiologic disturbance was suspected. She continued to have intermittent episodes of transient loss of consciousness until July, 1964, when she experienced the onset of [illegible]

From the Department of Medicine, Indiana University School of Medicine [illegible] Heart Research [illegible] the Marion County General Hospital, Indianapolis [illegible]
Supported by the [illegible] C. [illegible] Fund [illegible] Heart Association [illegible] part) by U.S. Public Health Service Training Grant [illegible] part) by facilities provided by Cardiovascular Clinical Research Center Grant H-4304 from the National Heart Institute, U.S. Public Health Service.
Received for publication June 24, 1966.
*Address: Krannert Heart Research Institute, Marion County General Hospital, 960 Locke [illegible] Indianapolis, Ind. [illegible]

nterval has increased to 0.60 second (fifth strip).

Figure 2 is reproduced to confirm that sustained 1:1 A-V conduction was dependent upon the S-A rate remaining at 100 per minute or less. The two strips in each row are sections from one continuous tracing. In the top row the strip on the left shows a P-P interval of 0.76 second, which shortens to 0.60 second in the right hand strip with the onset of complete A-V block. The bottom row shows a complete A-V block with an idioventricular rhythm and a P-P interval of 0.48 second. In the strip on the right the P-P interval gradually prolongs to 0.58 second, at which time two P waves are conducted. When the P-P interval reaches 0.60 second, sustained 1:1 conduction is again established.

Despite medical therapy, the syncopal attacks became more frequent and of longer duration. In an effort to prevent the attacks the patient underwent an operation for the implantation of a Medtronic artificial cardiac pacemaker. The pacemaker unit was implanted into the subcutaneous tissues of the anterior abdominal wall and the electrodes were attached to the epicardial surface of the left ventricle in the apical region. On the first postoperative day the ECG revealed a normal sinus rhythm and multiple pacemaker captures. The patient did well and she was discharged within 10 days. Two weeks after discharge she was readmitted because of a recurrence of symptoms of congestive heart failure. An ECG now revealed multiple pacemaker captures and frequent premature ventricular beats coupled to both the sinus and pacemaker complexes. Digitalis was administered for treatment of the congestive heart failure. On the evening of admission the patient suffered a Jacksonian seizure and a brief period of ventricular fibrillation was noted on the monitor, but this reverted spontaneously to the previous rhythm. On the following day persistent ventricular fibrillation occurred and vigorous attempts to resuscitate the patient were of no avail.

## Discussion

The sudden transitions from normal sinus rhythm to complete A-V block in this patient were unusual in that the underlying mechanism involved an acceleration of the S-A rate. Gilchrist[7] has emphasized the increase in block which occurs in second-degree A-V block, Type II, with acceleration of the atrial rate. However, previous reports relating to the mechanisms underlying Adams-Stokes attacks as a result of sudden transitions from a prevailing sinus rhythm to complete heart block have given more emphasis to the role of vagal influences upon A-V conduction.[1-4] There was evidence for considerable vagal effect upon the S-A node in the form of a sinus arrhythmia with P-P intervals as short as 0.48 second (lower left strip of Fig. 2) and as long as 0.76 second (upper left strip of Fig. 2). The A-V block was initiated, however, when the S-A rate was accelerating and the heart rate reached 100 per minute with a P-P interval of 0.60 second. The re-establishment of a sinus rhythm with a sustained 1:1 response was likewise dependent upon prolongation of the P-P interval to 0.60 second. The complete heart block in this case can best be explained on the basis of an abnormal prolongation of the refractory period of the A-V junctional tissues. When penetration

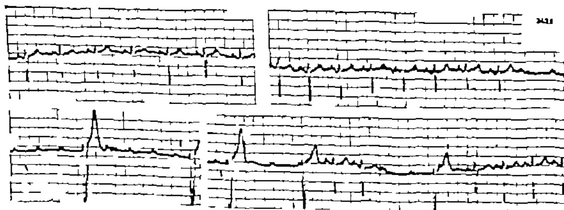


Fig. 2. The two strips in each row are sections from one continuous tracing. The top row illustrates shortening of the P-P interval at the onset of complete A-V block. The bottom row shows complete A-V block with idioventricular rhythm at left and the resumption of 1:1 conduction at right when the P-P interval is 0.60 second.

of the atrial impulse into the junctional tissues reached a rate of 100 per minute, the maximal rate at which the A-V junctional tissues could transmit impulses was exceeded.

Although reestablishment of a sustained 1:1 conduction was dependent upon a prolongation of the P-P interval to 0.60 second or greater, it was also dependent upon the first P wave after an idioventricular complex falling within an R-P interval of 0.46 to 0.56 second. In fact, as demonstrated in Figs. 1 and 2, one and at times two consecutive P waves were conducted at a time when the P-P interval was less than the apparent maximal rate of impulse transmission for the A-V junctional tissue. One explanation for this phenomenon is that the P waves were conducted within this R-P interval because they arrived at the A-V conduction system during the supernormal period set up by retrograde conduction of the idioventricular excitation wave.[13] It is unlikely, however, that supernormality of the junctional tissues could account for the sustained 1:1 conduction when the P-P interval varies from 0.60 to 0.78 second. The more likely explanation for this unblocking effect of the idioventricular complexes was first described by Wolferth[14] who reported a case of complete A-V block in which isolated P waves falling within an R-P interval of 0.45 to 0.74 second after an idioventricular complex were conducted. Noting that the immediately preceding P wave fell within or just before the idioventricular complex, he postulated that this P wave was blocked high in the A-V node by concealed retrograde conduction of the idioventricular complex. This allowed for a longer recovery period for the A-V conduction system, resulting in conduction of the next P wave. In our case the 1:1 response was then sustained if the maximal rate of impulse transmission of the A-V conduction system was no longer exceeded.

This patient gave a good history of an exacerbation of her syncopal attacks after the administration of digitalis, and the dangers of digitalis in this form of the Adams-Stokes syndrome have been emphasized.[1] It is also of interest to note that she had an increase in the frequency and severity of the syncopal episodes after the administration of Isuprel during her first hospitalization here. Schwartz and Schwartz[11] have pointed out that when normal sinus rhythm prevails during symptom-free intervals in patients with the Adams-Stokes syndrome, the administration of sympathomimetic drugs may lead to an exacerbation of the episodes of heart block. If, in this case, Isuprel exerted an accelerating effect on the S-A node without a proportional influence on A-V conduction, the tendency to A-V block would be increased.

The surgical approach to therapy with pacemaker implantation was also unsatisfactory in this patient. The poor results obtained from pacemaker implantation in the presence of sinus rhythm have been emphasized by others.[1,15] Although the mechanism initiating the terminal ventricular fibrillation was not recorded, the induction of repetitive ventricular arrhythmias as a result of artificial pacemaker stimuli in the presence of incomplete A-V block has been documented by Tavel and Fisch.[16]

## Summary

Acceleration of the sinoatrial rate leading to complete heart block is reported as an unusual cause of the Adams-Stokes syndrome. It is postulated that the maximal rate of impulse transmission of the atrioventricular conduction system was exceeded when the atrial rate reached 100 per minute, and complete heart block resulted. The reestablishment of 1:1 A-V conduction was dependent upon the atrial rate slowing to 100 per minute or less.

Many of the clinical features which tend to characterize individuals with the Adams-Stokes syndrome in whom normal sinus rhythm predominates between syncopal attacks were evident in this patient. The diagnosis was delayed because of the transient nature of the syncopal attacks and the cardiac arrhythmias responsible for them. Medical therapy, once initiated, failed to decrease the frequency or severity of the Adams-Stokes attacks. In fact, there was the suggestion that Isuprel led to an exacerbation of the episodes of heart block, presumably by increasing the atrial rate. The surgical implantation of an

artificial cardiac pacemaker was followed by the appearance of multiple ectopic ventricular premature beats and by ventricular fibrillation as a terminal event

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# Asymptomatic giant cell granulomatous myocarditis

*Ward M. O'Donnell, M.D.*
*Richard H. Mann, M.D.*
*Lancaster, Pa.*

Giant cell myocarditis is an uncommon postmortem finding, with only 23 cases reported in the English literature. About half of the patients in whom the morphologic change was seen died suddenly and unexpectedly. The remainder followed a course of rapidly progressive refractory congestive heart failure associated with a high incidence of cardiac arrhythmias.

Giant cell myocarditis is a disease of unknown etiology, and its differentiation from granulomatous myocarditis has been questioned. The relationship of this form of myocarditis to the structural alteration seen in syphilis, sarcoid, tuberculosis, Fiedler's myocarditis, systemic fungus, or protozoan disease is unsettled. The extracardiac involvement seen in some cases of giant cell myocarditis, in which associated granulomas are found in the lungs and regional lymph nodes, tends to remove this disease from the realm of an isolated myocarditis. The striking observation of giant cells of either the Langhans type or of myogenic origin in the fibrous granulomatous tissue separates this morphologic entity from the more common degenerative or inflammatory lesions of the myocardium. In fact, it is unusual to have giant cell formation as part of the reparative process in any heart lesion other than in the known chronic infective granulomas.

Our interest in this problem was stimulated by a recent patient whose death was unrelated to his cardiac function but whose heart at autopsy showed the pathologic changes of giant cell granulomatous myocarditis. This patient never had symptoms which could be related to an underlying cardiac disease. The purpose of this report is to emphasize that giant cell myocarditis may exist in the absence of symptomatic heart disease, that the morphologic process may be protracted with death occurring from intercurrent disease, that the involvement of *multiple organs can occur*, and that this pathologic change can be seen in the elderly as well as in the young. Finally, the histopathologic changes in the kidneys in this case lend support for a hypersensitivity etiology.

## Case report

A 76-year-old man was admitted to the Lancaster General Hospital with a 10-day history of slurred speech followed by aphasia, lack of comprehension, and finally stupor. There had been a history of typical grand mal type seizures for several years. The seizures were controlled by Dilantin. There was no history of head injury. The patient was known to have been diabetic for 5 years and was controlled by diet and Orinase.

A history was obtained of intermittent migratory pain in the joints covering a 50 year period and associated with episodes of red, painful, swollen joints. Movement of the knees and ankles had been limited. The clinical picture was that of gouty arthritis, and blood uric acid levels up to 10.3 mg. per cent had been recorded. The only medication used was aspirin. There was no history of exertional dyspnea, chest pain, or hypertension.

From the Departments of Pathology and Medicine, Lancaster General Hospital, Lancaster, Pa.
Received for publication Feb. 4, 1966.



Fig. 1 Myocardium showing focal replacement by granulation tissue. The giant cells are of the Langhans and foreign body types. Magnification ×100



Fig. Nodular proliferation of fibroblasts in the lung. Giant cells and lymphocytes are part of the cellular exudate. Magnification ×100

O . . . the . . . with phl . . . the right arm and leg . . . the left arm . . . of the left . . . The right pupil was . . . No . . . were present . . . present . . . on the right. Clonus of the left . . . elicited. . . . Babinski reflex . . . patient was unaware of painful stimuli . . . of the right side of the face. The heart was normal to auscultation and the lungs . . .

Fig 3 Interstitial m nonuclear cell infiltrati n between the tubules of the kidne  Th exudate al  con  ist d of a few plasma  ll   d   inophils Magnif  ti n ×400

Fi  4 Aortic valve  how  fibroplasi  and mononuclear cell infiltrati n M gnif  ti n ×100

clear There was some stasis dermatitis of the lower legs The left knee was slightly swollen The temperature was 101 F the pulse was 90 per minut and the blood pressure was 140/80 mm Hg

Initial laboratory studies were as follows hemoglobin 14 4 Gm  hematocrit 41 per cent white blood cell count 15 430 per cubic millimeter The differential showed 83 per cent polymorphonuclear leukocytes  3 1 1 10 lymphocytes  1  eosinophil  and 5 monocytes  Urinalysis   pecific gravity 1 0 5 albumin 1 plus The blood glucose was 200 mg per cent and the blood urea nitrogen was 61 mg per cent The blood serology for syphilis was negative A portable chest x-ray film showed mild cardiac enlargement and prominence of the left ventricle The lung fields were clear The impression was on admission

lar to the findings on a previous chest x ray examination performed 5 years before

The patient was given intravenous glucose with in lm coverage antibiotics and intramuscular Dilantin De pata fluid and adequate renal output the blood urea nitrogen rose rapidly to 210 mg per cent The temperature returned to normal on the day after admission The pulse rate remained in the range of 80 per minute and was regular The blood pressure varied from 140/78 to 120/70 mm Hg throughout his stay in the hospital The course in the hospital was one of progressive deterioration with rapidly developing azotemia The patient died on the seventh hospital day

*Autopsy findings* The body was that of a well nourished and well-developed 76-year-old white man The body length was 172 cm and the weight was estimated to be 185 pound Stasis dermatitis was present in the lower extremities particularly in the ankle region Pressure sores and cutaneous ulcerations were seen in the dependent portions of the body

The heart weighed 530 gram and the left ventricular wall was 1 mm in thickness The myocardium was brown with focal replacement by several pale yellowish gray areas in the left ventricular wall Mild fibrous thickening of the mitral and aortic leaflet was observed Both lungs together weighed 1 120 grams and the parenchyma was reddish-gray and of increased consistency The parietal and visceral layers of the pleura were adherent on the right side The spleen weighed 400 gram and had white fibrous plaques in the capsule The liver weighed 1 500 grams When the skull was opened a massive subdural hematoma was found on the left side Moderate pressure atrophy of the left cerebral hemisphere of the brain was noted

The histopathologic study was most revealing particularly in the material from the heart Multiple sections from the heart showed focal replacement of muscle by granulation tissue The granulation tissue was of the type usually seen in the protracted course of a chronic infective granuloma fibrous tissue containing many lymphocytes a moderate number of monocytes plasma cells and eosinophil The striking feature in these lesion was the presence of many multinucleated giant cell of the Langhans myogenic and foreign body types in which the cytoplasm lacked asteroids Schaumann bodies or fungi The inflammatory tissue was seen in the form of nodules replacing myocardial fibers and forming an interstitial pattern with surviving heart fibers at the periphery The epicardium was uninvolved but ul endocardial inflammatory and ? were evident The aortic valve leaflets were slightly thickened because of fibroplasia and infiltrations of polymorphonuclear leukocytes lymphocytes and plasma cells were seen in the substance Giant cell were not observed in the valve The proximal portion of the thoracic aorta contained heavy aggregation of lymphocytes and plasma cell in the adventitia

In the lungs there were granulomatous nodules showing fibroplasia plasma cells and lymphocytes in addition to giant cell of the Langhans type In the remainder of the parenchyma small nodules consisting of plasma cell and lymphocytes were

observed in the alveolar walls Acid fast and periodic acid Schiff stains of heart and lung tissue were negative

The left kidney weighed 330 grams and the right 200 grams The parenchyma was swollen and soft with reduced corticomedullary demarcation Microscopically a heavy diffuse interstitial inflammatory exudate was observed mainly in the cortex The infiltrate consisted of lymphocytes plasma cell and some eosinophils a few polymorphonuclear leukocytes were seen in some of the distal tubules

Essential pathologic diagnoses included old left sided subdural hematoma moderate pressure atrophy of the left cerebral hemisphere chronic giant cell granulomatous nodules involving heart and lungs moderate concentric hypertrophy of the left ventricle of the heart chronic fibrous pleuritis on the right side moderately advanced generalized arteriosclerosis and acute interstitial nephritis

## Comment

Chronic giant cell granulomatous myocarditis is a rare disease and only 2 of 23 recorded cases were seen by the same investigators the remaining 21 instances were individual case presentations The infrequency of the lesion accounts in part for its obscure etiology and our lack of understanding of its pathogenesis This granulomatous process must be considered to be a systemic disease since 10 of the 23 cases described involved extracardiac sites lungs aorta tonsils and Fallopian tubes[1] It is by no means an isolated myocarditis In our patient the granulomatous change was seen in the lungs in addition to the heart

This disease is seen in relatively young people the median age of listed cases was 34 years It has been reported in a 6-month old baby[2] Our patient (76 years) is the oldest individual reported to have this condition only one other case occurred beyond the fifth decade

Although our patient had the morphologic changes seen in giant cell granulomatous myocarditis he died from unrelated disease massive subdural hematoma and a rapidly progressive renal insufficiency He had no symptoms which could be related to his cardiac pathology The lack of symptoms is not unusual since in half of the recorded cases there was sudden death without previous warning It is probable that the heart muscle was involved by the granulomatous process to a lesser degree in our case than in those previously reported in the literature If our patient

had not died from intercurrent disease, there might have been a critical progressive destruction of myocardial tissue resulting in cardiac disability. He would then have been subject to sudden death or fatal rapidly developing congestive failure. It is also probable that the inapparent heart lesions existed for some time, since the pathologic changes were those usually associated with protracted inflammation. In the cases reviewed in the literature, the structural changes were in keeping with a chronic inflammatory disease state. Cardiac dysfunction apparently is related to the degree and location of myocardial damage, but our patient demonstrated that giant cell myocarditis may exist for some time before the terminal catastrophic illness.

No specific etiological agent has been incriminated in the pathogenesis of giant cell myocarditis. Rab and others consider the morphologic change to represent a host tissue reaction to any one of several possible agents. *Mycobacterium tuberculosis*, leprosy, syphilis, fungi, protozoa, or helminths. To date, spirochetes, tubercle bacilli, or known fungi have not been identified in the tissues by special staining methods. We suspect that mycologic cultural studies have been inadequate, since this rare disease is usually diagnosed after microscopic study. Collyns also viewed the anatomic changes as representing a deep-seated fungus infection or a hypersensitivity state.

Our patient had a rapidly developing azotemia which can be accounted for by the interstitial inflammatory change in the kidneys. Acute diffuse interstitial nephritis has been regarded generally as a complication of systemic septic states of bacterial or viral origin. It has also been related to hypersensitivity or allergic reactions to sulfonamides. Lederer and Rosenblatt[7] have described granulomatous interstitial nephritis characterized by giant cells, mononuclear cells, eosinophils, and polymorphonuclear leukocytes in the interstitial areas of the kidneys as an allergic response to sulfonamides. Although the infiltrate in the interstitium in the kidneys of our patient did not contain giant cells, there was a cellular exudate consisting of lymphocytes, plasma cells, eosinophils, and polymorphonuclear leukocytes. We ascribe these renal changes to a possible hypersensitivity reaction, and think that this mechanism might also be responsible for the pathogenesis of the granulomatous lesions seen in the heart and lungs. This opinion would support Collyns[4] who suggested the possibility of a hypersensitivity reaction on the basis of observed morphologic lesions in his reported case, and Tilmer and Michael[3] who considered the same causal relationship because of the giant cell arteritis observed in the myocardium in their patient.

A clinical observation relating to a hypersensitivity etiology should be mentioned in reference to a case of granulomatous giant cell myocarditis which was reported from the Massachusetts General Hospital. It concerned a patient who had received oral penicillin therapy and developed a "serum sickness" type of reaction and an exfoliative dermatitis which suggested a hypersensitivity reaction. In the treatment of the dermatitis over a period of 5 months, the patient received steroids in dosage which were sufficient to produce a Cushingoid appearance at the time of his final illness, a rapidly developing progressive congestive heart failure with tachycardia. The necropsy showed the changes of giant cell granulomatous myocarditis with a total lack of tissue repair. Either this was not a hypersensitivity reaction with respect to the pathogenesis of the myocarditis, or the steroids were incapable of reversing the process. However, from a therapeutic viewpoint, if this entity is suspected, it seems to be rational that treatment should include the use of large dosages of steroids. This seems to be especially true because of the catastrophic course of the disease.

## Summary

A 76-year-old man who was known to be an epileptic died from a massive subdural hematoma and a rapidly progressive renal insufficiency. Incidental findings at necropsy were the histopathologic changes of giant cell granulomatous myocarditis and granulomatous nodules in the lung. The patient had never had symptoms relating to his underlying cardiac pathology. It is postulated that the degree of myocardial involvement was not extensive enough to

interfere with cardiac function and an intercurrent fatal episode precluded the usual progression of this disease. Chronic giant cell granulomatous myocarditis is part of a systemic disease of unknown etiology. However, the renal lesions of acute interstitial nephritis seen in our patient lend support for a hypersensitivity mechanism. We think that this is the oldest patient to be reported on, and the only one in whom the cardiac pathology was not the cause of death.

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# Treatment of hypertension with antihypertensive diuretic drugs

*Robert J. Wolf, M.D.**
*Milton Mendlowitz, M.D.*
*Julia Roboz, B.S.*
*Stanley I. Gitlow, M.D.*
*New York, N.Y.*

Several categories of diuretics have been employed for the treatment of hypertensive disease. They are (1) the mercurial diuretics, (2) the benzothiadiazine and phthalimidine diuretics, (3) the carbonic anhydrase inhibitors, (4) the aldosterone antagonists, and (5) the unsaturated ketone derivatives of the aryloxyacetic (phenoxyacetic) acid diuretics. These therapeutic agents, which increase the renal excretion of salt and water, represent highly significant achievements in medical pharmacology in recent years. Furthermore, the mechanisms involved in the renal transport of water and electrolytes have been clarified by investigations of the mode of action of these drugs.

Over 50 years ago Ambard and Beaujard[1] first recognized the importance of the dietary restriction of salt in the treatment of hypertension. Since that time, it has been generally accepted that a reduction in the dietary intake of salt is important in the therapy of hypertensive disease. Although Ambard and Beaujard[1] incriminated dietary chloride in the pathogenesis of hypertension, it was Grollman and associates who attributed the hypotensive effectiveness of the dietary restriction of salt to the dietary restriction of sodium and implicated the importance of the low intake of sodium of the Kempner rice diet in reducing the blood pressure.[2]

In spite of the fact that rigid restriction of the oral intake of sodium does reduce the blood pressure, the inability of patients to accept this therapeutic regimen has resulted in its virtual abandonment. As early as 1945 it was reported that mercurial diuretics have a hypotensive effect,[3] but it was not until the benzothiadiazine diuretics were introduced in subsequent years that antihypertensive therapy with diuretic agents became recognized.

In order to understand the effects of the hypotensive diuretics on the kidneys, it is necessary to appreciate the physiologic mechanisms involved in the renal excretion of salt and water. Three mechanisms of reabsorption of sodium by the kidney exist: (1) sodium chloride transport, (2) sodium for hydrogen exchange, and (3) sodium for potassium exchange.

*Sodium chloride transport.* Sodium is

From the [illegible] Hypertension [illegible] and Hypertension [illegible] of the Department of Medicine [illegible] Meyer Division [illegible] The Mount Sinai Hospital, New York, N.Y.

Supported by Research Grant HE 05-04 (CV) [illegible] National Institutes of Health, United States Public Health Service.
Received for publication Jan. 4, 1967.

*Address: Mount Sinai Hospital, 100th St. [illegible] Fifth Ave., New York, N.Y. 10029.

reabsorbed against an electrochemical gradient in both the proximal and distal regions of the nephron including the distal convolutions and collecting ducts[3] Reabsorption of chloride follows passively Reabsorption of sodium chloride in the proximal segment of the renal tubule quantitatively exceeds that occurring in the distal segment An osmotically equivalent quantity of water is reabsorbed in the proximal segment of the renal tubule and reduces the volume of the glomerular filtrate by approximately 80 per cent The ascending limb of the loop of Henle is relatively impermeable to water thereby resulting in a significant concentration gradient between the hypotonic fluid remaining in the lumen of the renal tubule and the medullary interstitial fluid

*Sodium for hydrogen exchange* Sodium for hydrogen exchange also occurs throughout the entire course of the renal tubule Renal tubular cellular carbonic anhydrase enhances the reaction of CO and water to produce carbonic acid which rapidly dissociates to yield hydrogen ion and bicarbonate Hydrogen ion is exchanged for renal tubular lumen sodium which is returned with the bicarbonate to the extracellular fluid

*Sodium for potassium exchange* Sodium for potassium exchange occurs in the distal segments of the renal tubule after the sodium for hydrogen exchange has been virtually finished[4,7] The exchange of sodium for potassium is the principal method for the excretion of potassium The adrenal cortical hormones particularly aldosterone regulate this process which is dependent upon the availability of sodium in the distal segments of the lumen of the renal tubule

*Mechanisms of water reabsorption by the kidney* An important feature of the renal regulation of water balance is the counter current multiplier and exchange system This system allows the formation of high concentrations of solute in the interstitium of the renal medulla[8,9]

During hydropenia the osmolality of the proximal tubular fluid is iso osmotic with plasma renal tubular fluid at the bend of the loop of Henle is hypertonic and the renal tubular fluid in the first portion of the distal convolution is hypotonic and becomes isotonic as it proceeds down this segment of the renal tubule Antidiuretic hormone secreted during hydropenia increases the permeability of the distal convolution and collecting duct to water Renal interstitial hyperosmolality permits reabsorption of water from the distal convolution and collecting duct thereby resulting in hypertonic urine

During water diuresis renal tubular fluid entering the first portion of the distal convolution is hypotonic In the absence of antidiuretic hormone the distal segments of the renal tubule are impermeable to water and the renal tubular fluid remains hypotonic It is important to remember that the renal tubular fluid in the first portion of the distal convolution has a constant osmolality therefore the total quantity of solute reaching this site governs the total quantity of water delivered to the distal convolution

*Mercurial diuretics* The mercurial diuretics produce natriuresis proximal renal tubular sodium reabsorption is inhibited and chloride reabsorption which follows passively is also inhibited thereby resulting in natriuresis and chloruresis The urinary excretion of chloride may exceed the urinary excretion of sodium as a result of the sodium for hydrogen and sodium for potassium exchanges thereby resulting in hypochloremic alkalosis Inhibition of proximal renal tubular sodium reabsorption results in the presentation of a large quantity of water and solute to the distal renal tubular segments thereby resulting in an increase in free water clearance The excretion of potassium may be increased after the administration of mercurial diuretics in congestive heart failure by an enhancement of the quantity of sodium delivered to the sodium for potassium exchange renal tubular sites

Although parenteral mercurial diuretic therapy does reduce the blood pressure the need for frequent injections makes this form of treatment impractical The oral mercurial diuretics are less potent than the parenteral compounds Drug idiosyncrasy gingivitis and gastrointestinal distress are not infrequently observed side effects

*Benzothiadiazine and phthalimidine diuretics* The benzothiadiazine diuretics have

distal and tubular site of action. During water diuresis they reduce the rate of formation of solute-free water. They do not inhibit the production of a maximally concentrated urine and do not decrease the reabsorption of solute-free water during hydropenia. This evidence suggests that these compounds have their predominant action in the distal convoluted tubule.

During the past several years the structure of chlorothiazide has been altered, yielding many congeners which comprise the thiazide diuretic group. All of these thiazide diuretics may be used interchangeably. When employed in maximum dosage they have equivalent effects on both the excretion of sodium and the reduction in blood pressure. There is no apparent superiority of any one of these compounds to the others. All of them may produce depletion of potassium after prolonged administration.

The mechanism of action of the hypotensive effect of the benzothiadiazine drugs is unknown. A reduction in plasma volume and cardiac output may be responsible for the initially observed moderate hypotensive effect; nevertheless, the hypotensive effect persists despite re-expansion of the plasma volume.[3] Similarly, the hypotensive effect persists after the prolonged administration of these drugs when plasma volume returns to pretreatment level. The increased reactivity of the digital blood vessels to pressor substances in the hypertensive subject is decreased after the administration of the benzothiadiazine diuretics, probably because of depletion of sodium. Other investigators have implicated decreased vascular smooth muscle action,[3] altered sodium ion gradients,[17] and decreased responsiveness to infused norepinephrine.[3]

The advantages of the benzothiadiazine and phthalimidine diuretics in the treatment of hypertension are these: (1) they are potent and effective orally, (2) tolerance rarely develops, (3) toxic and side effects are fairly unusual, and (4) they potentiate other antihypertensive drugs. A unique property of these drugs is their relatively unimpaired diuretic efficacy in the presence of hypochloremic alkalosis and depletion of sodium.

Toxic symptoms and side effects are occasionally seen with the benzothiadiazine and phthalimidine diuretics. With each of these drugs the incidence is approximately the same. Weakness, easy fatigability, and mild gastrointestinal distress have been reported. Hyperuricemia with episodes of acute gouty arthritis and hyperglycemia are the most troublesome side effects. Maculopapular, petechial, and purpuric skin eruptions have been described. After the administration of these drugs the blood urea nitrogen may increase. Azotemia usually occurs in patients with reduced renal function. The loss of potassium may result in a deficit in total body potassium with concomitant clinical manifestations which might enhance the development of digitalis intoxication. The hypotensive response of a therapeutic dose (100 mg. daily) of hydrochlorothiazide may be equaled by the combination of hydrochlorothiazide (50 mg.) and the potassium-sparing pteridine diuretic triamterene (100 mg. daily) without the kaliuresis which occurs with the administration of benzothiadiazine.[3, 18] Neutropenia, pancreatitis, and photosensitivity are other reported side effects.

The benzothiadiazine and phthalimidine diuretics are particularly useful in combination with other antihypertensive drugs. The hypotensive effects of guanethidine, hydralazine, the Rauwolfia serpentina derivatives, and the ganglionic blocking agents are enhanced by the concomitant administration of these hypotensive diuretic agents.[19]

*Carbonic anhydrase inhibitors.* In 1940 Mann and Keilin demonstrated that sulfanilamide inhibited carbonic anhydrase. It was subsequently demonstrated by Schwartz[3] that the administration of sulfanilamide to patients with congestive heart failure resulted in increased renal excretion of sodium and loss of weight. Acetazolamide was introduced for clinical use as a result of these observations. After the administration of acetazolamide there is an increase in the excretion of sodium concomitant with a decrease in the reabsorption of bicarbonate, thereby resulting in an alkaline urine associated with an extracellular acidosis. The excretion of potassium is also increased as a result of the sodium-for-potassium exchange which

occurs in the distal portions of the renal tubules. Increased renal excretion of potassium may persist in the absence of continued increased renal excretion of sodium with the prolonged administration of acetazolamide.

The antihypertensive activity of the carbonic anhydrase inhibitors is modest and roughly parallels their natriuretic action. There is little or no increase in the diuretic natriuretic and antihypertensive properties of acetazolamide when the dose is increased above 500 mg daily. The renal loss of potassium that results from the administration of acetazolamide may produce clinical signs and symptoms of hypokalemia and potentiate the possibility of digitalis intoxication. Drowsiness, paresthesias, gastrointestinal distress, fever, leukopenia, anemia and depression of bone marrow are other reported side effects of the administration of acetazolamide. Refractoriness to the administration of acetazolamide may possibly be inhibited by the intermittent administration of the drug.

*Aldosterone antagonists.* The aldosterone antagonists, steroidal 17-spironolactones, are similar in structure to aldosterone. The most useful of these compounds is spironolactone, which inhibits the effects of aldosterone and desoxycorticosterone, thereby producing increased excretion of sodium, reduced excretion of potassium, loss of weight and hypotension in patients on a restricted intake of sodium.[4] The effects of spironolactone or aldosterone are reversed by the progressive administration of desoxycorticosterone in animals, thereby implying that these substances compete for the same renal receptor sites.

When compared to the natriuretic effect of chlorothiazide and the mercurial diuretics, that of spironolactone is relatively modest. After the administration of spironolactone maximum effectiveness is achieved in approximately days and after the drug is discontinued its therapeutic action may persist for a similar length of time. When administered in conjunction with either the benzothiadiazine diuretics or the mercurial diuretics it may potentiate the diuretic action of these drugs and it is of interest to note that when it is administered in conjunction with the mercurial diuretics there may be a potentiation of the inhibition of the excretion of potassium. The hypotension associated with the administration of spironolactone is not due to the depletion of body sodium or contraction of plasma volume since the hypotensive effect is not reversed by experimental correction of these situations. The hypotensive action of spironolactone has an onset later than its natriuretic effect.[14, 4] The magnitude of the antihypertensive action of spironolactone is comparable to that of chlorothiazide.[7]

Conflicting reports have claimed that spironolactone enhances the antihypertensive effect of the benzothiadiazine diuretics and other antihypertensive drugs,[11, 12] does not cause a significant decrease in blood pressure when studied in subjects controlled with placebos,[8] does not enhance the hypotensive effect of reserpine or guanethidine[20] and does enhance the antihypertensive effect of reserpine.[8] In order to resolve these disquieting observations we have performed a double blind study in which we compared the antihypertensive effect of spironolactone in low (25 mg daily), medium (100 mg daily) and high (200 mg daily) dosage both alone and combined with hydrochlorothiazide (100 mg daily). The statistical analysis of the results demonstrated that 100 mg daily of spironolactone had the greatest hypotensive effect.[27]

The side effects associated with the administration of spironolactone are fewer than those seen with the administration of the benzothiadiazine diuretics. Spironolactone, in contrast to the benzothiadiazine diuretics, does not significantly impair carbohydrate metabolism or uric acid metabolism. When administered for prolonged periods of time in large doses weak estrogenic activity may be exhibited by spironolactone and enlargement of the breasts may result. Spironolactone may produce hyperkalemia in patients with renal insufficiency. The relative paucity of side effects combined with the significant hypotensive activity associated with the administration of spironolactone suggests that this drug has advantages over the benzothiadiazine diuretics in the treatment of hypertension.

*Aryloxyacetic acid diuretics.* The administration of the aryloxyacetic acid diuretics results primarily in natriuresis and chloruresis. There are no consistent significant deviations in the glomerular filtration rate or renal plasma flow. The sum of urinary sodium and potassium usually exceeds that of urinary chloride.[8] During water diuresis and in patients with diabetes insipidus, after the administration of aryloxyacetic acid diuretics the excretion of solute ($C_{osm}$) increases, providing evidence for inhibition of proximal renal tubular sodium reabsorption, and solute-free water ($C_{H_2O}$) decreases, thereby establishing a site of action on the distal portion of the renal tubule.[8,87] During hydropenia the aryloxyacetic acid diuretics do inhibit the production of a maximally concentrated urine and do decrease the reabsorption of solute-free water, thereby indicating a site of action at the ascending limb of the loop of Henle.[8] Quantitatively the drug is more potent at the proximal site of action than at the distal sites of action.[88]

The antihypertensive effect of the aryloxyacetic acid diuretics is roughly comparable to that of the benzothiadiazine or phthalimidine diuretics.[88,89,90] Unfortunately, the side effects after aryloxyacetic acid diuretic therapy are significant. Hypochloremic alkalosis, hypokalemia, hyperuricemia with acute gouty arthritis, and gastrointestinal disturbances are frequently encountered. The short duration of action of this drug necessitates frequent daily administration. The potentially forbidding side effects with an antihypertensive effectiveness inferior to that of spironolactone and the benzothiadiazine and phthalimidine diuretics make it doubtful that this agent will achieve by itself a lasting place in the treatment of hypertension.

## Summary

The (1) mercurial diuretics, (2) benzothiadiazine and phthalimidine diuretics, (3) carbonic anhydrase inhibitors, (4) aldosterone antagonists, and (5) unsaturated ketone derivatives of the aryloxyacetic (phenoxyacetic) acid diuretics are the diuretic drugs which have been used in the treatment of hypertension. The physiologic mechanisms involved in sodium chloride transport, sodium for hydrogen exchange, sodium for potassium exchange, and water reabsorption by the kidney have been described and related to the action of the antihypertensive diuretic drug.

The two groups of drugs which are employed frequently at present are the benzothiadiazine and phthalimidine diuretics and the aldosterone antagonists. Of these groups it appears that the aldosterone antagonists (spironolactone), which have few side effects and significant antihypertensive activity, have therefore some advantages over the benzothiadiazine and phthalimidine diuretics in the treatment of hypertension.

The secretarial assistance of Mrs. Eva Milanski is gratefully acknowledged.

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# Fundamentals of clinical cardiology

## Dynamics of blood flow in stenotic vascular lesions

*Simon Rodbard, M.D., Ph.D.**
*Duarte, Calif.*

A brief statement of normal arterial dynamics will serve as the basis for an analysis of the dynamics of stenotic vascular lesions.

### Normal caliber

A normal artery serves as a conduit for several times the normal resting flow with only minimal losses of pressure due to friction (Fig. 1). The volume flowing through a normal artery is determined nearly entirely by the degree of openness, i.e., conductance (rate of flow drop in pressure, i.e., the inverse of resistance) of the peripheral vessel.[1] When conductance increases, as in the hyperemia of exercise, the pulsations of the vessel walls are enhanced, as revealed by palpation of the arteries or by oscillometry. Since flow is laminar, vibrations are not produced and no bruit is heard.

Variations in the viscosity of the blood introduce no significant increase in losses of energy in such large vessels, although viscosity may affect flow through the arteriolar, venular, and capillary segments.

### Stenosis

Narrowed vessels are the sites of drops in pressure, vibrations, and the stimulation of processes which tend to eliminate these dynamic factors.

Arteries may be narrowed by intravascular plaques or collarlike narrowings, by impingement of ligaments or spurs which abut on the vessel wall (Hardin)[2] or even by excessive force applied against the vessel by a stethoscope bell (Fig. 2). Transitory stenosis by means of compression of arteries by a sphygmomanometer cuff is utilized clinically in the measurement of the blood pressure.

*Effect of peripheral vascular conductance.* The extent of the disturbance produced at an arterial narrowing varies with the vascular conductance of the tissues which the vessel supplies (Table I). When the flow of blood through the tissue is minimal, as in resting organs, a slight stenosis introduces no significant impedance to the rate of flow to the tissues, the drop in pressure at the orifice is negligible, and murmurs are absent.

*Autoregulation.* A persistent rise or fall in arterial perfusion pressure triggers intrinsic mechanisms in muscle, brain, kidney, and other tissues[3,4] which adjust the peripheral vascular conductance so that the rate of blood flow remains unaffected (autoregulation). Thus, the fall in perfusion pressure introduced by a partial narrowing of an artery is associated with an increase in the conductance of the tissue, with the result that the rate of delivery of blood remains unaffected. Such autoregulatory mechanisms can counteract the effect of slight to moderate stenosis on the rate of blood flow to a tissue.

This study was aided by Grant ... HE 03... from the National Heart Institute, ... Heart Association, ...
Received for publication June ..., 1967.
*Director of Cardiology and Cardiovascular Research, City of Hope Medical Center, Duarte, Calif., and ... Professor of Medicine, University of Southern California School of Medicine, Los Angeles, Calif.

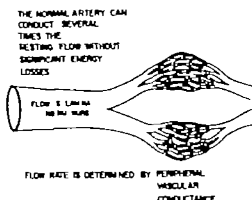



Fig. 1 Laminar flow in a large vessel Flow through vessel of normal caliber results in minimal losses of energy No murmurs are produced The rate of flow in such a system is determined by the conductance of the peripheral vessels and not by the characteristics of the vessel itself

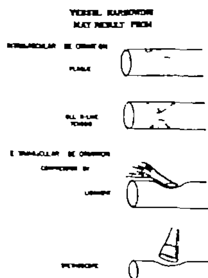



Fig 2 Vascular narrowing may result from intrinsic pathology of the vessel (upper two drawings) or as a result of deformation from without by ligament or pressure from a stethoscope (lower two drawings)

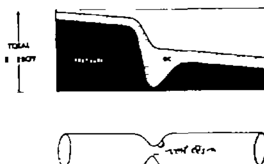



Fig 3 Effect of a stenosis on the distribution of hydraulic energy (above) in a vessel (below) At the upstream segment most of the energy is evident as pressure (black) a smaller amount is in the kinetic energy of velocity (dashed lines) and a small amount has already been converted to heat (stippled area) by friction, especially due to vortex formation At the orifice (shown in drawing of vessel) the velocity increases sharply at the expense of pressure and a significant portion is lost as heat Beyond the orifice the pressure rises although not to the prestenosis level and velocity approaches normal values The amount of energy converted to heat increases progressively

vessels even though the pressure in the arterial segment beyond the narrowing is less than normal An increase in activity of the tissue opens the vascular beds more widely and the pressure in the distal segment falls

*Effect of the narrowing* A narrowing impedes flow and a drop in pressure across the orifice becomes evident Flow through a stenotic orifice varies with the square root of the difference between the proximal and distal pressures[7] and with the orifice area The rate of flow does not keep pace with the drop in pressure Thus a doubling of the drop in pressure across an orifice increases the rate of flow by only 40 per cent ($\sqrt{200}$ per cent = 140 per cent)

When the vascular bed opens widely and the rate of flow increases greatly as after muscular exercise (Fig 3) the stenosis becomes the limiting factor in the delivery of blood to the active tissues The drop in pressure at the orifice and the velocity of the stream increase and vibrations are generated However as Ljrup has shown the oscillations of the poststenotic artery decrease This effect considered by some workers to be due to arterial spasm can be accounted for entirely on the basis of the decrease in the oscillations in pressure in the poststenotic arterial segment[8] associated with the increased peripheral vascular conductance of exercise

In moderate narrowing of an arterial orifice the drop in pressure across the stenosis is of greater magnitude the duration of the resulting murmur increases

*Table I. Hydrodynamic effects of a vascular narrowing*

| *Degree of narrowing* | *Pressure drop, velocity and murmurs* | | |
|---|---|---|---|
| | *Resting tissue* | *Active tissue* | *Very active tissue* |
| None | 0 | 0 | 0 |
| Slight | 0 | 0 | Systolic |
| Moderate | 0 | Systolic | Systolic and diastolic |
| Severe | Systolic | Systolic and diastolic | Systolic and diastolic; ischemic symptoms (fatigue, pain) |
| Complete | Ischemia (murmur restricted to collaterals) | | |

and the intensity and pitch exhibit crescendos as the aortic pressure rises in systole. During the falling arterial pressure of diastole the murmur decreases in intensity and pitch.[3]

In severe stenosis, a systolic murmur may be present even when the tissue is at rest. With the increased conductance of exercise the murmur is prolonged and extends into diastole. When the blood flow is inadequate to wash away the end products of metabolism, localized pain or fatigue and other ischemic disturbances become manifest. With complete obstruction of an artery, pulsations are absent beyond the narrowing and the murmur is no longer heard.

*Collaterals.* The marked difference in pressure at the junction of normal and ischemic tissues serves to increase flow through existing intercommunicating vessels and to stimulate the development of new vessels. These enlarge gradually in accord with the flow through them. These collaterals announce their inadequacy in the form of localized murmurs. When these collateral vessels are of sufficient size to deliver an adequate rate of blood flow so that the drop in arterial pressure is eliminated, the stenosed artery will decrease in size, as discussed below, and one of the new vessels will become the primary vessel of the tissue.

*Venous hums.* The laws that adjust vascular adequacy to the rate of flow operate in the veins as well as in the arteries. An inadequacy of the venous collecting networks and of the major venous channels is manifested in increases in pressure gradients, flow velocity, and the production of vibrations.[11] Venous hums are not uncommon in children during the rapid growth phase and when the general increase in metabolic activity enhances the volume of the venous return. The disproportion between vascular caliber and rate of blood flow is especially evident when the child is in the upright position; the drop in pressure from the veins draining the head to the subatmospheric pressure in the thorax may collapse the veins at the clavicle sufficiently so that murmurs and hums are heard over these vessels.[1]

Light pressure over the veins at the clavicle or placement of the subject in a reclining position reduces the drop in pressure and eliminates the venous hum, thereby readily differentiating the hum from arterial bruits originating in the adjacent arteries. The high right atrial pressure of right heart failure also distends the veins and inhibits the hum.

Venous hums are also heard at other sites at which the venous network is inadequate. For example, hum may be heard over the abdomen when the hepatic blood flow is deviated through subcutaneous collaterals. A similar dynamic pattern is heard during the period of rapid gestational growth of the uterus and its contents. The hums are enhanced with the drop in pressure during the inspiratory fall in pressure in the thorax and superior vena cava. The murmurs may diminish

with the reduction in the drop in pressure as the thoracic pressure rises during expiration The growth of anastomotic venous channels eliminates the drop in pressure and the bruit

*Flow through anastomoses* When arteries which supply different vascular beds are connected by anastomoses the rate of flow through each of the arteries is affected by the relative conductance of the two beds[11] and by the size of the anastomoses When one of the vascular beds opens widely the increased rate of runoff through it lowers the pressure in its main supplying artery The higher blood pressure in the anastomosing artery will then flow into the vascular bed which has the higher conductance and the tissue of lower conductance may receive an inadequate supply of blood Thus in a limb with a partially stenotic arterial supply opening of the cutaneous vessels by the application of heat to the skin deviates blood from the muscles which are thereby rendered even more ischemic

Attention has been called recently to the ischemic symptomatology which results when a narrowing at the root of the subclavian artery limits the rate of the flow of blood to the arm (Fig 4) During rest no effects may be noted However the marked increase in vascular conductance produced in the muscles during exercise of the arm can drain off some of the blood from the circle of Willis

Exercise of the arm may thus precipitate an episode of cerebral ischemia an effect known as subclavian steal

Effects of this type which are more generally appreciated include the deviation of aortic blood through a ductus arteriosus and thence through the high conductance of the pulmonary vascular bed (Table II) Coarctation of the aorta beyond the ductus increases the deviation and lead to ischemia of the vessels of the lower limbs

When the blood pressure in the two arms differs by more than a few millimeters of mercury palpation may establish a significant asynchrony of the pressure waves at the radial or brachial arteries The indirect measurement of blood pressure in the two arms or of the delay in the transmission of the arterial pressure wave quantifies the severity of such an ...

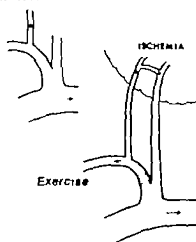



Fig 4 Steal syndrome At rest (*upper left*) flow through the aorta (*horizontal arrow*) is distributed among the subclavian (*left*) and carotid arteries The carotid (*upper*) vessel and vertebral arteries supply the brain through the circle of Willis In the drawing at right a severe stenosis is shown in the subclavian artery When exercise opens the vessel of the arm some of the blood moving toward the head is deviated across the circle of Willis to the vertebral artery and runs off into the high conductance of the vessels of the arm If the blood flow to the brain is compromised symptoms of cerebral ischemia will ensue

*Table* II *Steal syndromes*

| Stenosis | Ischemia |
|---|---|
| 1 Subclavian + arm exercise | → Cerebral |
| 2 Femoral arterial + heating of skin | → Leg muscle |
| 3 Coarctation of aorta + ductus arteriosus | → Lower extremities |

tion We have observed a number of patients with marked differences in pressure timing and duration of the arterial Korotkoff sounds in the two arms However the presence of such murmurs and other evidence of stenosis of the arteries to an arm is not necessarily associated with cerebral ischemia or the imminence of a cerebrovascular occlusion The gradual modifications in vascular caliber which are induced by hydrodynamic forces may account for the benign course of this abnormality in some patients

## Hydrodynamic forces and vascular caliber

The occasional tendency for the progression of a localized stenosis,[10,11] the proliferation of collateral vessels, and the development of poststenotic dilatations have been attributed to the operation of hydrodynamic forces. The effects of the pressures on the walls of the vessels have excited the continuing interest of physiologists, pathologists, and clinicians. In earlier studies, this laboratory had discussed the possibility that local drops in pressure and increased velocities, the ingrowth of the vascular lining with a resultant progression of the stenotic tendency, is facilitated. This thesis has subsequently been restated by others.[12-14] However, although the pressures in all of the arteries of the body are approximately equal, the caliber of these arteries vary enormously from that of the aorta to that of the small arteries. The concept that changes in pressure affect vascular caliber is therefore without basis.

The caliber of most blood vessels varies directly with the size and activity of the vascular bed being supplied.[8] This correlation as well as the tendency to progression of stenosis and poststenotic dilatation have recently been shown to result from the interaction of the stream with the wall (hydrodynamic drag).[1,2]

As a laminar stream moves through a blood vessel, the central (axial) fluid moves with relatively high velocity. Adjacent enclosing sleeves of fluid move at progressively lesser velocities. The sleeve of fluid adjacent to the wall (boundary layer) moves at minimal velocities but exerts a shearing force (hydrodynamic drag) on the endothelial cells (Fig. 5).

When peripheral vascular conductance increases, the velocity of all of the laminae increases, the drag of the boundary layer which acts on the endothelium also increases. It is known that an increase in the rate of flow through a vessel is associated with an immediate increase in its caliber.[3] This effect can be attributed to the increased drag on the endothelium which apparently stimulates a localized dilation of the smooth muscle of the vessel wall. If the increased flow is persistent, the vessel will tend to be reorganized

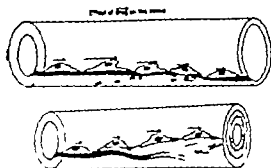


Fig. 5. The role of hydrodynamic drag in the determination of vascular caliber. In the upper drawing, the first arrow indicates a normal drag acting on an endothelial cell. With increased drag, shearing stress is applied to the endothelial cell, which causes the vessel to widen acutely. This decreases the velocity of the stream and reduces drag to normal values. If the increased drag is persistent, the lumen of the vessel is reorganized around a larger lumen. The force of drag is indicated by the horizontal arrows. In the lower drawing, a reduced rate of flow results in a subnormal drag force (short arrow at left). The lumen of the vessel is decreased, thereby increasing the velocity and the drag force to normal values. The vessel is then reorganized around the reduced lumen.

around the larger lumen. Conversely, a reduction in peripheral vascular conductance reduces the velocity and drag of the stream, and endothelial-medial relationships[**] reduce the vascular lumen. If the reduced drag persist, subendothelial proliferations and general vascular reorganization take place around a reduced lumen (Fig. 5).

A change in the drag forces on the wall thus can be considered to activate feedback mechanisms which return the drag forces to normal values. This mechanism of normal vascular growth and atrophy can thus account for the fine adjustment of the caliber of the vessel with the blood flow through the tissues it supplies.

Depending on local circumstances, the foregoing blind mechanical forces may also operate to induce progressive enlargement or progressive stenosis, either of which can threaten the integrity of the tissue or even of the individual.

*Poststenotic dilatation.* At a narrowing, flow generates high velocities which destroy laminarity and produce vortices and turbulence in the downstream vascular segment. In a region of such nonlaminar flow

drag increases out of proportion to the volume of blood flowing through the vessel. Poststenotic dilatation can thus be attributed to the chronically increased drag beyond a region of narrowing.

*Progressive narrowing.* Hydrodynamic patterns can induce a progression of the stenotic process at the point of greatest narrowing in a stenosis. This effect may be attributed to the hydrodynamic conditions at the downstream end (nozzle) of a narrowing. Fluid is accelerated as it passes through the nozzle of a narrowing, gaining momentum in accord with the increase in velocity. At the downstream tip of the nozzle the high momentum of the stream lines continues to move them inward toward the central axis of the stream, thereby separating the stream from the vessel wall. The interaction of stream and wall and the hydrodynamic drag on the endothelium are minimal at such a site of separation. As mentioned above, subendothelial proliferation appears at sites of reduced drag. The tip of a stenotic nozzle is therefore a locus of increased rate of growth and thus of progressive stenosis. At some sites, as at a ductus arteriosus or a ventricular septal defect, such an ingrowth with a consequent closure of the connection may prove to be beneficial. In other sites this stenotic tendency may threaten limb and even life itself.

## Summary

A normal artery can serve as a conduit for many times the resting flow without significant loss of energy or production of murmurs. In such vessels the rate of flow is determined primarily by the peripheral vascular conductance (rate of flow/drop in pressure) rather than by the characteristics of the artery.

In a system of vessels connected in series the rate of flow is limited by the segment of lowest conductance. Thus when the conductance of the peripheral vascular bed is low, a partially stenotic lesion has no effect on the rate of flow. When an arteriovenous fistula or an increase in metabolic activity markedly increases the delivery through an arterial narrowing, the stenotic segment becomes the limiting factor and a systolic bruit indicates that the stream is no longer laminar. Thus a murmur is the announcement that the caliber of a vessel or valve is inadequate to provide for laminar flow. With further increases in peripheral vascular conductance and rate of flow, the murmur increases in intensity, pitch, and duration.

Cross flow is minimal in an anastomosis between two parallel arteries which deliver blood to separate vascular beds of equal conductance. If a stenosis is present in one of the arterial roots, blood will shunt from the normal vessel to the vascular bed of the narrowed vessel. If the stenosis is severe, the deviation of blood will be marked and the tissues normally supplied by the normal vessel will become ischemic (steal syndrome).

The interaction (hydrodynamic drag) of the stream with the vessel wall determines vascular caliber. Laminar streams interact normally with the wall. The separation of the stream lines from the wall at the downstream lip of a stenotic orifice produces a locus at which stream-wall interaction is minimal, with the result that the narrowing becomes progressively marked. In the poststenotic segment turbulence increases the interaction of stream and wall and stimulates a localized enlargement (poststenotic dilatation).

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# Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Alan F. Lyon

## Reappraisal of digitalis. Part III. Electrophysiology of digitalis action

*Alan F. Lyon, M.D.**
*Arthur C. DeGraff, M.D.***
*New York, N.Y.*

The effect of the digitalis glycosides on the electrical activity of the heart is closely linked to the effect on the sodium-potassium pump. The electrophysiologic effects of digitalis in the intact subject are exceedingly complex and until recent years largely unexplained. That digitalis can produce almost any arrhythmia is well known. The variety and apparent unpredictability of these reactions to digitalis can be explained by two different factors.

*1.* The first factor is concerned with the electrophysiologic differences between the various parts of the heart. Functional differences exist between the sinoatrial node, the specialized conducting tissue in the atrium, the ordinary atrial myocardium, the upper, mid, and lower portions of the atrioventricular node, the bundle of His, the Purkinje fibers, and the ordinary ventricular myocardium. Thus each of these parts of the heart responds to digitalis differently.

*2.* The second factor in the intact heart is the additional effect of digitalis that is mediated through the autonomic nervous system. It has long been known that digitalis either produces vagal stimulation or increases sensitivity to vagal discharge. The vagus-mediated action of digitalis can produce electrical effects that are sometimes similar and sometimes dissimilar to the direct effects of digitalis. It has also been suggested that some of the "direct" effects of digitalis are actually mediated by pro-adrenergic or anti-adrenergic effects rather than through direct effects on membrane electrolyte movement. This "adrenergic" hypothesis is still controversial since the experiments that suggest it are physiologically quite complex, involving reserpinization, beta-adrenergic blockade, and/or surgical ablation of the sympathetic nervous system. Nonetheless, whether these studies demonstrate a key role of the sympathetic nervous system in the mediation of digitalis effect or only a permissive role, they make it clear that changes in catecholamines can profoundly modify the electrical effects of digitalis.

It is remarkable, in view of all this complexity, that anything has been clarified about these actions of digitalis. The tool that has been most useful in developing some understanding of these phenomena is the intracellular electrogram, which is recorded by a tiny glass electrode that can be inserted atraumatically into any cardiac cell. With this electrode the intracellular electrical potentials during and between each cardiac cycle can be recorded. When

Received for publication Aug. 9, 1966.
*Chief, Cardiology Section, [illegible] Veterans Administration Hospital, Bronx, N.Y.
**Professor of Therapeutics, New York University College of Medicine, and Consultant in [illegible], [illegible] Veterans Administration Hospital, Bronx, N.Y.

the potentials recorded are compared with those from an extracellular electrode in the extracellular space, a record of the gradients in potential across the cell membrane can be obtained. When such a device is used to record potentials in isolated strips of the various types of cardiac tissue bathed in digitalis, a precise assessment of the response of each tissue to digitalis can be made. Through comparison of the results obtained in this manner with the studies of the whole heart with and without innervation and with studies in the intact human being, some conclusions can be drawn about the total electrophysiologic effects of digitalis.

*Action on undifferentiated ventricular myocardium.* The intracellular electrogram when recorded from strips of tissue of undifferentiated ventricular myocardium driven at slow rates demonstrates prolongation of the last rapid phase of repolarization (comparable to the T wave of the clinical electrocardiogram). An increase in excitability, that is, a decrease in the quantity of electrical stimulation necessary to produce a propagated response, can also be shown. This stage of direct effect cannot be consistently documented in the intact heart, in which it would be manifested by an isolated prolongation of the relative refractory period. The first direct effect on the ventricular myocardium that can be detected in the intact heart and that occurs in the isolated strip at higher doses of digitalis is a shortening of the action potential due to a reduction in the plateau or phase of slow repolarization (equivalent to the S-T segment of the clinical electrocardiogram). Despite the over-all shortening of the action potential, the rapid repolarization portion of the action potential is prolonged. These effects lead in the intact heart to a decrease in the absolute and an increase in the relative refractory period.

This stage of effect of digitalis on the ventricular myocardium is also associated with decreased excitability. With still higher doses of digitalis there is a decrease in the resting potential of the ventricular myocardium, which leads directly to a decrease in the speed and size of the action potential. The clinical correlate of this is a decrease in conduction velocity.

*Action on undifferentiated atrial myocardium.* The data on the direct effects of digitalis on the ordinary atrial myocardium are less conclusive than those on the effects on the ventricle. It would appear that at low doses there is a slowing of repolarization and prolongation of the action potential. This results in prolongation of the effective and relative refractory periods in the intact heart. These same doses slow conduction velocity and depress excitability. Higher doses in isolated strips show rapid repolarization and shortening of the action potential. Unlike the situation in the ventricular myocardium, the direct effects of high doses are not easily documented in the intact heart, but the effects of low doses related to a prolonged action potential are prominent in the intact heart.

*Action on the Purkinje fibers.* The response of the Purkinje fibers to digitalis is similar to that of the ventricular myocardium, with two major exceptions. (1) All of the effects occur at relatively lower doses of digitalis, so that, for instance, severe conduction disturbances may be present in the Purkinje system when conduction in the ventricular myocardium is still normal. (2) The Purkinje fibers differ from ordinary myocardium in that they have a subsidiary pacemaker function, which is due to a gradual loss of resting potential during diastole. This can ultimately lead to spontaneous electrical discharge of the fiber if it is not discharged first from without. This loss of resting potential is called slow diastolic depolarization. The characteristic of spontaneous discharge is called automaticity and is common to all pacemaker tissue.

The effect of digitalis on Purkinje fibers differs from that on ordinary myocardium in that the drug also affects slow diastolic depolarization. It leads to an increase in the rate of such depolarization and to an increase in automaticity. This may ultimately lead to discharge prior to the sinus pacemaker and to ventricular premature contractions and ventricular tachycardia. Finally, the shortening of the refractory period that occurs in the Purkinje system is quite uneven, so that recovery time varies from fiber to fiber. These variations in recovery and conduction in the Purkinje

system can lead to differences in the sequence of repolarization in different parts of the heart. This is the cause of the digitalis-induced S-T changes of the clinical electrocardiogram.

*Action on the sinoatrial node.* Like the Purkinje fibers, the sinoatrial node is specialized pacemaker tissue that manifests slow diastolic depolarization. It differs from the Purkinje fibers in that it is less rather than more sensitive than the surrounding myocardium to the direct effects of digitalis, and in that the direct effect that does occur is a decrease rather than an increase in automaticity due to prolongation of slow diastolic depolarization.

*Action on the atrioventricular node.* Perhaps the most important electrical action of digitalis is to decrease conduction through the atrioventricular node. Digitalis produces a measurable increase in the effective refractory period of atrioventricular nodal tissue in the intact heart. This is apparently not due to an increase in the duration of the action potential but to a failure of propagation of the impulse. In this situation the portion of the atrioventricular node stimulated may actually depolarize but conduction is so poor that the impulse is not transmitted to nearby cells from which it can be recorded. Thus this prolongation of the effective refractory period is actually a conduction effect.

*Vagal action of digitalis.* The vagal action of digitalis, that is, those effects on the electrical activity of the heart that are produced by either increased vagal stimulation or increased responsiveness to vagal stimulation, is limited to the area of vagal innervation: the sinoatrial node, the atria, and the atrioventricular node. The important vagal effect on the sinoatrial node is the same as the direct effect, a decrease in automaticity due to a slowing of slow diastolic depolarization. The vagal effect on the ordinary atrial myocardium, on the other hand, is opposite to the major direct effect in that it leads to shortening of the absolute and relative refractory periods. Only the upper and mid portions of the atrioventricular node are sensitive to vagal stimulation. In these regions the effect is similar to that produced directly by digitalis, leading to a further interference with conduction.

*Net effects on the innervated heart in the areas innervated by the vagus.* The net effect of moderate doses of digitalis on the innervated heart reflects primarily the vagal actions of the drug. There is a decrease in sinoatrial automaticity, a decrease in atrial excitability, a shortening of the effective refractory period, a slowing of conduction in the atria, and a depression of the transmission of impulses in the atrioventricular node. Below the atrioventricular node the direct effects are predominant. Thus there is an increase in the automaticity and a decrease in the conductivity of the Purkinje fibers and a decrease in the conductivity, excitability, and refractoriness of ventricular myocardium.

*Electrophysiologic effects on the human heart.* Except in the presence of atrial fibrillation, in which case the decrease in conductivity in the atrioventricular node is helpful in controlling the ventricular rate, the electrophysiologic effects of digitalis have little clinical influence in the therapeutic range and become important only when toxic doses of the drug produce arrhythmias. What can be seen with therapeutic doses are sagging S-T shifts reflecting a shift of the vector of slow repolarization away from the QRS. These changes may or may not involve the T wave, which sometimes shows peaking and sometimes shows inversion. In any case, these repolarization changes have poor correlation with either therapeutic or toxic effect.

The slowing of the sinus rate frequently produced by digitalis in lower animals is not seen in normal man, in whom no change in the resting or exercise rate can be documented. The only evidence of increased vagal activity that can be found in normal man is an increase in the frequency of sinus arrhythmia. The decrease in pulse rate that occurs with digitalization in patients with congestive heart failure probably reflects an increase in stroke volume rather than a direct electrophysiologic effect. *The increase in pulse rate on standing, recorded after injection of* lanatoside C, probably reflects a decrease in venous return. An increase in the [illegible]

interv al does not occur con i tenth The increased autom aticity of Purkinje fibers that occurs at slow rates i not important so long as the rate of sinoatrial discharge i faster and there i no heart block

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## Differential actions of polypeptides and other drugs on coronary inflow vessels

Considerable controversy exists as to whether vasopressin and its synthetic analogues cause arterial and venous smooth muscle to contract. Such knowledge of the differential vascular effects of these neurohypophyseal polypeptides is necessary for at least two reasons: (a) the suggestion that these hormones may play a role in the local regulation of blood flow via modulation of vascular smooth muscle responsiveness to other neurohumoral substances and (b) their possible therapeutic value in the treatment of shock.[11] Although these neurohypophyseal polypeptides exhibit selective and paradoxical effects in the microcirculation,[3] which are beneficial in experimental shock,[11] some of these analogues have been reported to induce marked coronary arterial constriction and arrhythmias in dogs, guinea pigs, and rabbits.[14] Such detrimental effects if found on the human myocardium would obviate the use of these drugs clinically. PLV 2 (2-phenylalanine-8-lysine vasopressin), on the other hand, has been reported (a) to increase the relative myocardial blood flow in rats and (b) to be antiarrhythmic in the cat and free from inducing arrhythmias in man.[17]

In view of the foregoing species differences, it was thought to be worth while to examine the influence of 8-arginine vasopressin and PLV 2 on isolated coronary arteries divorced from the in vivo effects of myocardial metabolism. However, because of possible segmental differences in coronary arterial reactivity, we thought that it was advisable to examine all three major coronary inflow vessels (right coronary, left coronary, and circumflex arteries).

Freshly removed bovine beef hearts (within 10 to 15 minutes after slaughter) were washed and placed in normal mammalian Ringer solution (8.6 Gm. NaCl, 0.3 Gm. KCl, and 0.33 CaCl per liter). After being dissected from the myocardium, helical strips (4 by 25 mm.) of all three arterial types were prepared and suspended isometrically under 1 gram of tension and incubated in 50-ml. muscle chambers containing Krebs-Ringer bicarbonate solution (composition in millimoles per liter: NaCl, 125.0; KCl, 4.7; $NaH_2PO_4$, 1.18; $MgSO_4 \cdot 7H_2O$, 1.18; $NaHCO_3$, 25.0; glucose, 0.35; $CaCl_2$, 2.52; EDTA, 0.026) at 37.5° C. through which 95 per cent $O_2$ and 5 per cent $CO_2$ was bubbled. Force of contraction was measured with a Sanborn FTA 10-1 transducer and recorded on a heat-writing oscillograph (Sanborn Model 150). Two hours after the preparations were incubated under tension, the effects of various drugs were examined. A total of 70 preparations dissected from 5 hearts was utilized for the present report.

Vasopressin (8-arginine vasopressin, up to 1.0 U. per milliliter) or PLV 2 (up to 0.5 U. per milliliter) failed to induce contractions in any of the different coronary strips. However, both vasopressin and PLV 2 (Fig. 1, A) produced relaxation in *all three* types of vessel after all segments were induced to contract with a variety of tension-developing substances, e.g., histamine, serotonin, KCl, acetylcholine, and angiotensin. BaCl-induced contractions, however, could not be relaxed by vasopressin or PLV 2. It should be mentioned that relaxations induced by PLV 2 were greater than those induced by vasopressin in respect both to magnitude and rate.

Although contractions were induced in all three segments with KCl, BaCl, or histamine, the three types of vessel exhibited wide differences in sensitivity (Fig. 2). Acetylcholine (up to 50 µg per milliliter) and angiotensin (up to 50 µg per milliliter) induced contractions only in circumflex segments, whereas serotonin had no contractile effect on left coronary strips (Fig. 2).

Norepinephrine, epinephrine, and the nonapeptide bradykinin caused only relaxations in all three types of vessel (Fig. 1, B). It should be noted that both the degree and rate of relaxation in all cases was limited by the amount of tension initially induced by the various contractile agents; the greater the initial developed tension, the less the rate and magnitude of the relaxation. Norepineph-

Supported in part by Grant HE-09012 [illegible] and [illegible] Public Health Service.

All [illegible] of drugs except for vasopressin and PLV 2 are [illegible] [illegible] Hoechst [illegible] [illegible] [illegible] obtained [illegible] NBC [illegible] [illegible] [illegible] [illegible] [illegible] BaCl, KCl [illegible] [illegible] [illegible]

[illegible] PLV 2 and [illegible] were supplied through the courtesy of Dr. B. Berde [illegible] [illegible] N. J.

r n (pe n l t l ppr imat l 10 times pc in ot pinephrin w ht l r in pro du ng con ns rcl n n This relative potency mil r t th r eport H ther f r h nn ry t ri (see f Fr 18) The acetylcholine or bradykinin lk s pr nd FLV 2 m er n l l t t f n l the o n ry trip

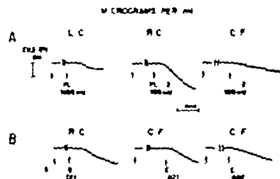



Fig 1 A and B Responses of bovine left coronary (L C) right coronary (R C) and circumflex (C F) arterial strips to FLV 2 fr bkin (B) pinephrine (E) and nor phinephrine (NE) after the es tabl hment of to ntr tion f the admin trat n of 6.0 μg per milliliter of h t m (H) or 4.0 μg per milliliter of serotonin (5 HT) t the muscle chamber

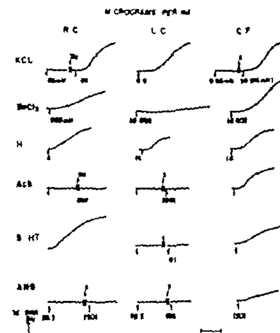



Fig 2 Comparison of contractile activity of different coronary arterial segments to KCl BaCl histamine (H) acetylcholine (Ach) and serotonin (5 HT) L C Left coronary artery R C Right coronary artery CF Circumflex artery

contrary t th t reported f r epinephrine and or norepinephrine on large coronary rteries in the d The sterchol mine induced relaxations uld be selectively and consistently inhibited by premcu bating the strips with the beta adrenergic blocker dichloroisoproterenol HCl (0.007 μg per milliliter) These findings probably indicate that these vessel l k re ptor and that catech lamine induced relaxations of bovine coronary arteries may be medi ted by beta adrenergic receptor

It is ident from these data th t vasopre in and at le t one of its synthetic analogues FLV 2 l n it elic t ontractil responses in any of the three major bovine coronary inflow el However quite ntrary to report for some other mammalian species[11] the neurohypophyse l polypeptides induce r l xation of bovine coronary smooth muscle in all three types of conduit essels which may be mil r t the s l lat tion report l by Bord k f r post rior pituitary le le extr perfusion of the isolat l at heart The different sen t ities of the left right nd circumflex onary arteries how th t the smooth muscle cell f these essel cannot l n ler d be pharmacologi ll homog neous Similar example of thi het rogene t ha been reported by th rs f r s nes fr m other ascular bed In addition these d t uggest that pharmacologic recept r ites or r t e smooth muscle lls for ertain drug e g ang ten in acetylcholin nd ser t nin re lackin m dif f rent segment of the bovine ronary arterial t Last l our re ults point ut and reconfirm the f ndings f man other workers (too numerous to el bor te upon here) th t it important to define not nly the species but als the p rt ular ves l n( ) of a particular scular bed when referring to th pec f pharm odynamic action of drugs

Burton M Altura Ph D
Department of Anesthesiology
New York University School of Medicine
550 First Ave
New York N Y 10016

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# Rheumatic fever without clinical evidence of carditis

## The necessity and efficacy of chemoprophylaxis

Rh umatic fever w thout cl nical d nce of ar dti today account for o er one half of the total ep sodes of acut rheumatic f er nd in the adult acute rheumat fever is even more freq ently characterized by the bsence of card ti The pur pose f th tudy was to reve lnat patient wh had rheumatic f w thout l cal denc of ard t part cularl in regard t the p obabl t f conse p ences of rh umatic re urrences l the necessity n l efficacy of chemopr phyla

O r t l group con ted f 33 pat ent wh ha l acute rheum t fever w thout cl l dence f dit wh were be g followed t the Cmdy M o l Hosp t l C lnc Cl l the Georgia Heart Associat on Cardiac Cl nics th oughout the tate The control group was comprised f 312 patient who had t h um t fever w th card tis The diagn s f acut heumat fe er w mad n corda w th the mod fed J nes criteria an l ca d t w hagnosed by the def u n of the American Heart A sociat on Chemoprophyl x when g w adm te ed recommen led by the An a Heart A soc t

The g p of pat ent w thout cl l es fen f ca bt cons ted f 136 m les 54 Negr e and 82 wh tes an l 19( fem les 119 Neg es f 77 wh tes The erage age of the p tient t the t me of the init al att ck f t heumatic fev w 10 1 yea nd at the t me of the t f t w 17 years

A t tal f 9 f ... ent of the pat ent w th ...

Th t was supported by f nd f m the Card ... I ... C ... l C ... of the Georgia Departm nt of Publ H lth A la Ga

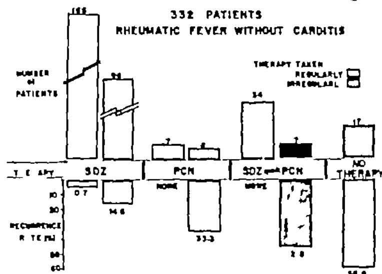



Fig. 1. See text.

rheumatic fever without clinical evidence of carditis had recurrent rheumatic fever with a total of 10.3 per cent recurrent episodes. The average age at the time of the rheumatic recurrence was 13.3 years with an average interval between the initial and recurrent rheumatic episode of 4.4 years. Eleven patients had the initial episode of acute rheumatic fever after 21 years of age and none of these patients had a rheumatic recurrence.

Both the initial and recurrent episodes of acute rheumatic fever were randomly distributed throughout the months of the year.

Of the 332 patients who had rheumatic fever without carditis (Fig. 1), chemoprophylaxis with sulfadiazine had been prescribed for 261 and with penicillin for 13, and 41 patients had been changed from sulfadiazine to penicillin or vice versa, usually because of drug sensitivity. Chemoprophylaxis had not been prescribed for 17 patients.

Of the 261 patients in the sulfadiazine group 165 took the drug regularly and 96 irregularly. Seven patients in the penicillin group took the antibiotic regularly and 6 irregularly. In the mixed sulfadiazine-penicillin group, in whom the medication had been changed because of drug sensitivity, 34 patients received the chemoprophylaxis regularly and 7 irregularly.

Only 1 patient had a recurrence of rheumatic fever while on regular chemoprophylaxis. There was a 0.7 per cent recurrence rate representing this one patient in the group taking sulfadiazine regularly, a 14.6 per cent recurrence rate in the group taking sulfadiazine irregularly, no recurrences among patients regularly on penicillin or mixed sulfadiazine-penicillin prophylaxis, and a 33.3 and 42.8 per cent recurrence rate respectively among the groups on penicillin irregularly and mixed sulfadiazine-penicillin prophylaxis irregularly. Note that over one half of the patients, 58.8 per cent, who were not prescribed chemoprophylaxis had recurrent rheumatic fever.

These data represent a total of 2,475 patient years of follow up of patients with rheumatic fever without clinical evidence of carditis—1,349 patient years of regular chemoprophylaxis and 1,126 patient years of irregular or no chemoprophylaxis.

These 332 patients who had acute rheumatic fever without clinical evidence of carditis were further characterized with regard to chemoprophylaxis (Table I). The 206 patients who were regularly receiving chemoprophylaxis were separated from the 126 patients who were receiving irregular or no chemoprophylaxis. The average age of the patients at the time of onset of rheumatic fever was 9.95 years in the group on regular chemoprophylaxis

*Table I. Three hundred and thirty-two patients with rheumatic fever without carditis*

| | *Regular chemoprophylaxis* | *Irregular or no chemoprophylaxis* |
|---|---|---|
| Number of patients | 206 | 126 |
| Average age at time of initial episode of rheumatic fever (yr.) | 9.95 | 10.03 |
| Average duration of follow up (yr.) | 6.55 | 8.9 |
| Recurrence (per cent) | 0.49 | 3.0 |

almost identical with the 10 03 years in the group on irregular or no chemoprophylaxis The patients receiving prophylaxis were followed for an a erage of 6 35 years a ignificantly greater average follow up 8 9 years was recorded for the group on irregular or no chemoprophylaxis Indeed ome patients in the latter group antedated the era of chemoprophylaxis for rheumatic fever

Only one patient in the group on regular chemoprophylaxis had recurrent rheumatic f er for a recurrence rate of 0 49 per cent In the group receiving chemoprophylaxis irregularly or not at all 29 patients had recurrent rheumatic fever for a recurrence rate of 23 per cent We believe that this markedly greater recurrence rate i due to the omission of chemoprophylaxis and cannot be explained merely by the longer duration of follow up

In our group of 332 patients who e initial attack of acute rheumatic fever was not associated with clinical e idence of carditis the rheumatic recurrences ter ded to be of a mimetic nature i e pa tients who did not have carditis with the initial rheumatic epi ode did not ha e carditi with the recurrent episode We ha e followed only one pa tient whose recurrence was not mimetic he had rheumatic polyarthritis without carditi at age 6 and t a e 24 he had recurrent rheumatic fever characterized by arthritis by pericard ti (manifested by friction rub) and by myocarditi (manifested by A V dissociation on the electrocardiogram) at present it has been 5 years since the recurrent episode and he has shown no residual alvlar damage

The sex race and age distribution of the control group of 317 patients with rheumatic fever with carditis was comparable to that of the group without clinical evidence of carditis However the group with carditis had s gnifica tly smaller recurrence rate of rheumatic fever than that of the group w th out cardit —4 2 as compared to 9 1 per cent These data appear to contradict the reports in the liter ature which show an increased recurrence rate of rheumatic episodes among patients with card ti However in our group w thout carditi ignificantly more patients either were not prescribed chemoprophylaxi or more commonly were not taking chemoprophylaxi regularly 38 per cent in the group ithout card tis as compared to 22 per cent n the group w th carditi The tudy group without clinical evidence of carditi th had a ignificantly greater number of patient receiving chemoprophylaxis irregularly or not t ll and a concomitant ig nificantly greater number of patients with recurrent rheumatic fever than did the control group with carditi

In summary a group of 332 patients whose initial epi ode of acute rheumatic fever w not a sociated with clinical evidence of card ti there was a recurrence rat of rheumatic fever of 9 1 per ent Recurrent epi odes occurred throughout the year and for a con iderable number of ears after the initial a ute episode Rheumatic recurrences were encountered almost ex lu i ely among patient receiving inadequate or no chemoprophylaxi Patients without clinical arditi during the nitial attack of acute rheumatic fever u ually escaped apparent cardiac damage during recurrent episodes the recurrences tended to be mimetic Long term year round chemoprophylaxi recommended to prevent the recurrence of rheumatic episodes in pat ent with rheumatic fever w thout clinical carditi de pite the pparent benign nature of the recurren e

*Nanette Kass Wenger M D*
*Robert Leonard M D*
*Ben Burn M D*
*Emory Un ersity School of Medicine*
*69 B tle St S E*
*Atlanta 3 Ga*

## Primitive bulbus cordis and idiopathic hypertrophic subaortic stenosis in man

The current empha of studies on the phy iologic mechanism and et ological understand ng of id opathic hypertrophic baortic tenos ha revived terest n th comparative anatomy nd phy ology f the bulbus cor i

The bulbus l b tus t n t structure with import t bearing m funct n hark The bulb co l ma tain ts l t nct anatomic tructu n l remain funct onall gnif cant through the repti le pecies C nemag ocard ogram m turtl l ha ks ha h wn a lat tole contraction of the bulbus cord and the persistence of contract on during diastole These f l re are observed in patients w th id opath hypertroph ubaort tenos It h been noted that the ntract on of the bulbu rd nonmamm l an pe es is exaggerated nder the fluence of ad renaline d ring aped be rt action f log mula functi nal beha ior in the right entr ula outfl w tract has been demon trated More recen report h l ated the use w th wh ch lef vent cular rtic grad ents ca be pr duced u

The operative mortality was 4 per cent and there was no operative death in the last 30 cases.

Of the total, 34 patients were traced and re-examined in 1965 after a mean postoperative interval of 7.2 years (8 for more than 10 years, 14 for 5 to 10 years, 12 for less than 5 years). Twenty-nine of these were found to be free from cardiac symptoms and leading normal lives, although 6 of them had residual atrial fibrillation or flutter and 2 had elevated jugular venous pressure. Of the other 5 who had symptoms at the time of review, 1 had rheumatic mitral incompetence and 1 was still improving after operation. Excluding simple arrhythmias, there was thus evidence of significant cardiac dysfunction in 15 per cent of those reviewed. Liver function was normal in all.

If adequate resection of the constricting tissues and avoidance of trauma to the coronary arteries are assumed, the main determinant of prognosis after successful operation must be the extent of the myocardial damage caused by the original disease. Atrophy of myocardial fibers after chronic constriction has been demonstrated both clinically and experimentally, but is usually considered to be reversible. If actual destruction of fibers had occurred with permanent impairment of function, it would be expected to reveal itself by progressive cardiac enlargement over the postoperative years. Thus the authors failed to find in the patients studied, only 2 of whom had cardiothoracic ratios over 0.5?. The electrocardiograms, which showed abnormal T waves before operation in nearly every case, reverted to normal in 40 per cent. The absence of regression is not to be interpreted as a poor prognostic sign, for the electrocardiographic changes of minor surface injury to the myocardium have been shown to predominate over those due to deep injury. Persistent T wave abnormalities are therefore not inconsistent with normal cardiac function.

The authors conclude that constriction, even when it has been unrelieved for several years, infrequently causes permanent damage to the myocardium. The outlook for at least 80 per cent of those operated on for constrictive pericarditis thus appears to be good, and successful relief of constriction is likely to prove to be a curative procedure.

*R. H. ?orkel, M.B., M.R.C.P.*
*Senior Registrar*
*Department of Cardiology*
*The Middlesex Hospital*
*Cleveland Street*
*London W. 1, England*

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**Handbook of Cardiology for Nurses.** By Walter Modell, M.D., F.A.C.P., Doris R. Schwartz, M.A., R.N., Louise S. Hazeltine, M.A., R.N., and Frederic T. Kirkham, Jr., M.D. New York, 1966, Springer Publishing Company, Inc. 323 pages. Price $4.75.

This fifth edition on cardiology for nurses outlines in a few pages some of the common problems and definitions in cardiology. The fact that the handbook has reached the fifth edition attests to its success and excellent reception and is evidence that an educational need is being met. However, from the reviewer's point of view, the book lacks advice on how to nurse the patient with heart disease and how to handle the special problems. The book is primarily a course in clinical cardiology which is presented very well in a few pages. The book does assist the nurse in understanding cardiology better. It is up to date and is supported by a few illustrations and a good index. It is hoped that the sixth edition will include extensive practical instructions and advice necessary to good nursing of the patient with heart disease. This book on cardiology is recommended to nurses as a valuable source of instruction on aspects of heart disease and its treatment.

**Second Symposium on Catecholamines.** Edited by George H. Acheson, M.D., reprinted from *Pharmacological Reviews*, Vol. 18, No. 1, March 1966. Published for the American Society for Pharmacology and Experimental Therapeutics by Williams & Wilkins Company, Baltimore, 1966. 803 pages. Price $15.

This is an authoritative summary of the pharmacology and physiology of the catecholamines. The symposium was held at the Istituto di Ricerche Farmacologiche "Mario Negri," Milan, Italy, July 4-9, 1965. Everyone who is interested in catecholamines will find this to be an excellent book. It is highly recommended as a very comprehensive and reliable source of information on an important subject.

**Conference on Pulmonary Circulation.** Oslo, 1965. Edited by Carsten Muller. Oslo, 1965, Universitetsforlaget. ? pages.

This is a summary of the symposium on the pulmonary circulation held in Oslo during September, 1965. The conference was concerned with six main topics, namely, pulmonary vasomotor regulation, physiology and pathophysiology of the pulmonary capillaries, pulmonary blood volume, pulmonary vascular bed, pulmonary function and pulmonary circulation in heart disease, and pulmonary hypertension. The participants were from Denmark, Finland, Norway, and Sweden. These papers therefore reflect Scandinavian work and thinking on a very important subject. There are two separate reports which are concise, though good and interesting. Each paper is followed by a summary of the discussion on all the aspects of the conference. This is a good book.

**L'Hypertension Artérielle** (Arterial Hypertension). Edited by Paul Milliez and Philippe Tcherdakoff. Paris, 1966, L'Expansion Scientifique Française. 524 pages.

This represents the proceedings of the first meeting of the International Club on Arterial Hypertension held July 5-7, 1965, in Paris. The proceedings include several papers on (1) hypertensive factors of the kidney, (2) hypotensive factors of the kidney, (3) aldosterone, (4) hypertension with renal artery lesions, and (5) hemodynamics. The conference as reflected in this book apparently was conducted much like the well-known and extremely successful Ciba Symposia. Many papers are included in this book with a bibliography and the discussions which followed the presentation of each paper. The texts are in English and French, more in the former language. Those who follow the field closely may, out of curiosity, wish to read the book to learn what transpired, but will find little new, whereas others who wish to learn the present concepts will find the book to be useful and a source of ideas for investigation. The book is nicely printed and bound in leather.

**Methods in Medical Research.** Volume 11. By Robert F. Rushmer, Editor-in-Chief. Chicago, 1966, Year Book Medical Publishers, Inc. 301 pages. Price $10.50.

This is a good handbook. The tradition of presenting brief discussions of current methods and related problems in medical research is maintained. Several brief, well-presented, and well-illustrated papers are concerned with the main topics in the pocket-sized handbook. The five topics discussed are (1) measurement of displacement and strain, (2) flow detection techniques, (3) force, tension, and pressure, (4) quantitative methods for investigating the microcirculation, and (5) neurophysiologic techniques. The contributors are experts in their respective fields, and the problems tackled are among the most difficult in physiology. This is a good handbook and is highly recommended to physiologists, physicians in cardiovascular diseases, and medical and graduate students.

## Book received

**Dietary Fat and Human Health.** A Report of the Food and Nutrition Board, National Academy of Sciences–National Research Council. Publication No. 1147. National Academy of Sciences, Washington. 5.31 pages. Price $1.50.

# Announcement

The Fourth Annual C[illegible] Seminar [illegible] Electrocardiography (diagnosis and [illegible] of electrocardiography and [illegible] therapy) sponsored by The Rogers Heart Foundation will be held at The [illegible] Bath Club, Redington Beach, Fla., Dec. 1 through 4, 1966.

Visiting faculty will include Edward Dorney, M.D., Atlanta, Ga.; [illegible] Nixon, M.R.C.P., London, England; Joseph [illegible], M.D., Washington, D.C.; Demetrio Sodi-Pallares, M.D., Mexico City; and Calhoun Witham, M.D., Augusta, Ga. The seminar will be directed by Henry Marriott, M.D., St. Petersburg, Fla.

For further details write The Rogers Heart Foundation, 500 [illegible] Bldg., St. Petersburg, Fla.

American Heart Journal

*December 1966 Volume 72 Number 6*

# Acknowledgment to reviewers

The Editors wish to express their thanks and appreciation to the following who have aided in the review of manuscripts during the past year

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George Adrouny
Earl Aldinger
Edward C. Andrus
D. M. Aviado
B. M. Baker
Samuel Bellet
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# Editorial

## The prevention of coronary heart disease

*Alexander R P Walker D Sc*
*Johannesburg South Africa*

In a recent investigation undertaken in London[1] the survival rates of two groups of patients with coronary disease were compared one on a reduced intake of fat and the other on their usual self chosen diet Since no advantage accrued to the experimental group the conclusion was reached that a low fat diet has no place in the treatment of myocardial infarction Others have voiced similar views It seems to be somewhat premature that an ineffective change in *one* factor of a disease known to have protean etiology should lead to the outright rejection of that single factor in the treatment of the disease Within the last generation there has been a legion of contributions seeking to elucidate apportion blame and make recommendations in relation to the different factors which promote or cause coronary heart disease (CHD) As is well known factors accepted as being of prime importance at least among Western populations are diet activity stress smoking hypertension and overweight Currently there are three main hypotheses each according dominant influence to a single factor namely (1) diet[6] (2) activity[7] and (3) stress[8,10] In respect to diet there is a difference of opinion concerning the influence of individual components namely (a) fat[4] and (b) sugar[11] and in relation to fat there is a division regarding the role of (i) saturated and unsaturated fats[4,1] and (ii) essential fatty acids[1,13]

Although some doubt the extent of the increase that has occurred in mortality from CHD[14] none is under any illusion as to the magnitude of the public health problem involved Among sophisticated populations the two highly practical questions at issue are these (1) Does a significant decrease in proneness ensue if the offending factor or factors (whether in excess or short fall) are modified or corrected? (2) Does it lie within the power of such populations to make the changes called for

In the first place it is well to face the somewhat ironic situation in which certain of the factors enumerated above may be observed to be operating singly or in combination among primitive technically retarded or unsophisticated populations and yet their presence is consistent with the virtual absence of the disease Such freedom is seen in the Navajo Indians in the Central African Masai Samburu[4] and Rendille[1] despite a high intake of fat and in the Mountain Apache in rural Japanese[18] and in Moroccan Jews in spite of considerable hypertension Such

F... S... Africa I... for Medical Research Johannesburg South Africa
Received for publication ... 1966

freedom is also seen in the South African Bantu. In urban areas there is a by no means insignificant moiety of individuals who outwardly at least have many of the same characteristics which are known to conduce to CHD in whites, yet the disease remains rare.[1,2] Evidently different populations in different contexts may react differently to a given stimulus, or as Lowenstein[3] has it, a factor or factors deleterious in one human context may be largely or wholly innocuous in another. This phenomenon is neither unique nor novel; it has counterparts in other spheres of human experience. For example, in Durban, South Africa, there is very roughly the same prevalence (about 10 per cent) of *Endamoeba histolytica* in the stools of Africans, Indians, and whites. In Indians and whites the organism lives commensally and is largely nonsymptomatic, but in Africans the organism is often present in a fulminating invasive form causing severe illness and sometimes death. What is it that, in one population but not in another, catalyzes or energizes a potentially noxious component to become malign?

This leads to another question. Does epidemiological information on populations in which CHD is very uncommon have any serious bearing on the changes required to alleviate proneness to CHD in *sophisticated* populations? Often it is regretted that if only we could adopt a feature or features of this or that primitive or other population, CHD would no longer be the enormous problem that it is today. But a white person does not become a Bantu just by lowering his intake of fat or his level of cholesterol, nor a Masai[7] simply by considerably increasing his habitual activity, nor upon request or with intention does he become relaxed and lose his CHD prone personality merely by resolving that it shall be so. I believe that the CHD prone segment of a population should aim at attaining the relevant characteristics of the CHD less prone segment of that same population rather than seeking to emulate this or that feature of other populations of the type mentioned.

Bearing in mind the hypothesis propounded, let us turn now to the main questions at issue. In a given CHD prone segment of population, how far can persons, perhaps late in life, even with the utmost willingness, project themselves into another context? There are groups with low prevalences of CHD, such as the elderly but very active Swiss mountain farm workers.[8] Can the relevant protecting features, including presumably their regular and tranquil manner of life, really be adopted? In a recent study in Norway,[77] it was shown that certain farming communities, as compared with the population of Oslo, have a *threefold* lower mortality rate from arteriosclerotic and degenerative heart disease and also from cancer. Can the sophisticated man of Oslo hope to take on the necessary protective features of the rural farm worker's life? Or can the elderly in Bucharest[11] incline toward the life led by the Danube delta fishermen? Then there are the Seventh Day Adventists.[1,10] Does adoption only of their diet, nonsmoking habits, etc., confer the lower prevalence of CHD that they enjoy? What of the role of their religion and philosophy? Crucially, in the segments of population mentioned as having lower CHD, just *what* features have to be taken on?

In recognition of our uncertainty over the answers to these questions, not to speak of the difficulties of conformation involved, the view held by many is somber indeed. Keys[n] has stated that, although "there is still no final proof that the reduction of serum cholesterol level . . . will substantially alter the risk of subsequently developing CHD . . . ," it is suggested as a possible prophylactic measure. In one evaluation of the Framingham study,[n] it is admitted that, despite an explosive expansion of research in lipid metabolism, very little is known of the principal determinants of regulation of serum cholesterol level. Morris[n] concurs, believing that "the etiology of high blood cholesterol remains an urgent problem on which both genetic and environmental data at present are grossly deficient." Russek[7] goes further and considers that "it seems unlikely that management directed solely at reduction of blood cholesterol without simultaneous efforts to neutralize psychophysiological mechanisms induced by environmental stress can be significantly effective." The regret expressed in a recent

review was that it will prove difficult to modify certain trends in sophisticated affluent communities.[34] In a World Health Organization Study Group Report[3] it was concluded that there is no effective means of reducing CHD. Another writer has averred that we are as helpless against the ravages of cardio-vascular degeneration as were our ancestors against plague.[35]

But are these views, which would seem to be the nadir of despondency, warranted? In certain countries in war time involuntarily imposed changes in diet, activity and pattern of life were associated with a strikingly abrupt fall in the death rate from ischemic heart disease.[4] The most apposite analogous but peace time situation known to the writer concerns white South African long term prisoners who conform in measure to the dietary pattern and manner of life of the Bantu. During confinement such prisoners have a negligible number of episodes of CHD or deaths due to it.[37] In the period 1960-1965 in the main prisons for long term offenders among 2 450 persons who were 20 years old and upward there was an annual average of 3 episodes of and 1 death from CHD. In an age matched male population in Johannesburg deaths were about 8 times more common. The low prevalence of CHD in the prisoners is in agreement with similar reports on inmates of federal penitentiaries.[38]

The burden of foreboding borne by the patient with coronary disease has been commented on in a recent editorial.[5] Despite the foregoing it is *not* believed that the outlook is hopeless. It is certainly not entertained that current investigations such as those of the Anti-Coronary Club and the National Diet-Heart Study[40] are not eminently worth while; they may well yield extremely valuable results. In the meanwhile the balanced recommendations both for the patient with coronary disease[41] and for the anxious or coronary-disease-prone person have been ably set out. Russek[1] has provided evidence which suggests that those who stop smoking considerably lower their proneness to CHD. Stamler[42] by no means rules out a breakthrough in research and has recently stated that "the ability to control the major risk factors by safe medical means holds out the very real possibility of achieving primary prevention of premature clinical atherosclerotic disease whether coronary, cerebral or peripheral".[43]

Nevertheless I am driven to consider that in spite of the knowledge available the bulk of the patients with coronary disease and certainly the bulk of the coronary disease prone moiety of the population either elect not to or cannot re-orientate themselves to the magnitude of the changes required of them for significant relief from susceptibility. It is considered that the *large scale* altering of the requisite factors for reducing proneness to CDH is scarcely possible in a free society; that this can only be achieved in situations in which a measure of coercion prevails,[44] as indicated in the two examples given.

Achilles said to Odysseus in Hades: "Rather would I be a slave in a pauper home and be above ground than be a king of kings among the dead." But in the times of Homer there were perils from famine and war and pestilence, and life was brief. Nowadays when far more people live much longer it would seem to be inescapable that most people prefer to continue to pursue their habitual way of life which at least has not the physical rigor of the past, and to accept the risks of degenerative disease which are implicit in the manner of life prevailing, risks which may well be increased by every milestone of socio-cultural economic advancement—the rapid growth of the middle class, the affluent society, the New Frontier, the Great Society.

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# Clinical communications

## Hemodynamic sequelae of atrial, ventricular, and sequential atrioventricular pacing in cardiac patients

*Philip Samet, M.D.**
*Cesar Castillo, M.D.*
*William H. Bernstein, M.D.*
*Miami Beach, Fla.*

Earlier studies from this laboratory have emphasized the role of atrial systole in the maintenance of ventricular function.[1-4] Comparable data have been obtained by others both in the experimental animal and man.[5-10] The aforementioned studies have demonstrated that atrial pacing results in larger cardiac outputs than does ventricular pacing at the same rate in subjects in sinus rhythm.[1,7-11] Since these differential effects of atrial and ventricular pacing may be due either to the role of atrial systole or to the role of aberrant ventricular depolarization, further studies were planned to differentiate between these two possibilities. The development of a paired pulse pacing unit (Medtronic) permitted utilization of a third type of pacing: sequential atrioventricular pacing. In this form of pacing, one stimulus is applied to a bipolar catheter in the right atrium and a second stimulus is applied to a similar catheter in the right ventricular outflow tract at a prefixed interval somewhat less than the normal P-R interval for that particular patient. In this fashion the normal relationship between atrial and ventricular mechanical activity is maintained but an aberrant pathway of ventricular depolarization must of necessity be utilized. Sequential atrioventricular pacing thus permits a decision as to whether the different effects of atrial and ventricular pacing are due to aberrant pathways of ventricular depolarization or to absence of synchronized atrioventricular activity in ventricular pacing.

### Materials and methods

Thirty-three patients with pulmonary emphysema with or without cor pulmonale and 27 subjects with rheumatic heart disease were studied. Eighty-nine comparisons of cardiac output during atrial, ventricular, and sequential atrioventricular pacing were made in the group with pulmonary emphysema: 7 at rates 60-89 beats per minute, 33 at rates 90-109, and 49 at rates 110-140. Eighty similar comparisons were made in the group with rheumatic heart disease: 15 at rates 60-89 beats per minute, 39 at rates 90-109, and 26 at rates 110-140. The three varieties of pacing employed were described above.

From the Section of Cardiology, Department of Medicine, Mount Sinai Hospital, Miami Beach, [illegible] University of Miami School of Medicine, Coral Gables, Fla.
Supported by [illegible] Public Health Service [illegible] Heart [illegible] HE-06901-03 [illegible] HE-09781-01.
Received for publication Feb. 22, 1966.
[illegible]

Two 3 1 125 cm long bipolar electrode catheters were passed one into the right atrium and a second into the right ventricle A third catheter was passed into either the pulmonary artery or the left atrium by the transseptal left atrial puncture technique to serve as a vehicle for injection of 2.5 to 3 mg of indocyanine green for indicator dilution determination of cardiac output The dye curves were inscribed by aspiration of blood from a systemic artery with an indwelling Cournand needle via a Harvard constant infusion withdrawal unit and Gilford densitometers The dye curves were recorded on an 8 channel Electronics for Medicine recorder and were calibrated by three dye in blood concentration levels The semilog replot extrapolation method was used to calculate cardiac output Measurements of flow were made at 1 to 2 minutes after the institution of any given rhythm

**Results**

The group with pulmonary emphysema will be discussed first The mean indices for the entire set of 69 studies were 2 60 2 06 and 2 53 L min M for atrial ventricular and sequential atrioventricular pacing respectively The difference between atrial and ventricular pacing was significant $p < 0.001$ the same was true for the difference between ventricular and sequential atrioventricular pacing The difference between atrial and sequential pacing was only significant at the 0 05 level $p = 0.0$ The essential data are plotted in Figs 1 3

For the 60 89 rate group the mean indices for the set of 7 for atrial ventricular and sequential pacing were 2 46 2 16 and 2 48 L/min M respectively The ventricular pacing index differed from the other two $p = 0.05$ There was *no difference* between atrial and sequential atrioventricular pacing For the 90 109 set of 33 observations the mean indices for atrial ventricular and sequential pacing were 2 58 2 00 and 2 48 L min/M respectively The ventricular mean index differed from the other two $p < 0.001$ Atrial and sequential pacing levels were also significantly different but only at the $p = 0.05$ level For the 110 140 set of 49 observations the mean indices for atrial

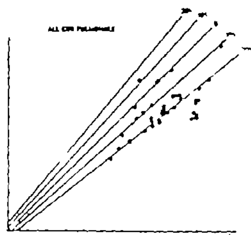



Fig 1 Comparison of cardiac indices during atrial and ventricular pacing at all three groups of heart rates studied The zero line is the line of identity Ten and 20 per cent are deviations from the line of identity The patient group is that of pulmonary emphysema and/or cor pulmonale

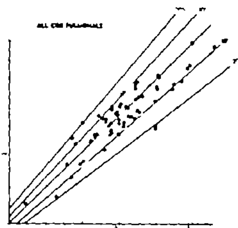



Fig 2 Comparison of cardiac indices during atrial and sequential atrioventricular pacing

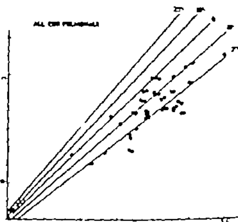



Fig 3 Comparison of ventricular and sequential atrioventricular pacing in patients with pulmonary emphysema and/or cor pulmonale

ventricular and sequential pacing were 2.63, 2.09, and 2.57 L/min/M² respectively. Ventricular pacing levels were significantly different from the other two pacing levels, $p < 0.001$. There was no difference between atrial and sequential pacing.

The 80 observations in the group with rheumatic heart disease will be discussed next. The mean indices for the entire set were 2.79, 2.29, and 2.70 L/min/M² for atrial, ventricular, and sequential pacing, respectively. The ventricular pacing index was significantly different from the other two levels, $p < 0.001$. The differences between atrial and sequential pacing were different only at the 0.05 level, $p = 0.05$. These data are shown in Figs. 4-6.

For the 60-89 rate group, the mean indices for the set of 15 observations were 2.85, 2.42, and 2.74 L/min/M² for atrial, ventricular, and sequential pacing, respectively. The atrial and ventricular means differed, $p < 0.001$. The ventricular and sequential means differed, $p = 0.05$. The atrial and sequential means were not significantly different. For the 90-109 rate group, the mean indices for the set of 39 observations were 2.84, 2.32, and 2.71 L/min/M² for atrial, ventricular, and sequential pacing, respectively. The ventricular level differed from the other two means, $p < 0.001$. The atrial and sequential means also differed, $p = 0.001$. For the 110-140 rate set of 26 observations, the mean indices were 2.68, 2.18, and 2.65 L/min/M², respectively, for atrial, ventricular, and sequential pacing. The ventricular levels were significantly different from the other two levels, $p < 0.001$. The atrial and sequential means were not significantly different.

The electrocardiogram during sinus rhythm, atrial, ventricular, and sequential atrioventricular pacing is shown in Fig. 7. In 5 patients in these two groups (rheumatic heart disease and pulmonary emphysema), multiple measurements of cardiac index were made at repeated intervals after the institution of sequential atrioventricular pacing. At 0-2 minutes, 2-5 minutes, and 5-7 minutes, the average indices were 2.62, 2.48, and 2.69 L/min/M², respectively, demonstrating that valid measurements of flow may be made within 1 to 2 minutes

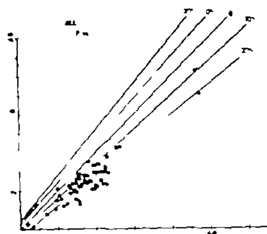


Fig. 4. Comparison of atrial and ventricular pacing at all three groups of heart rates studied in patients with rheumatic heart disease.

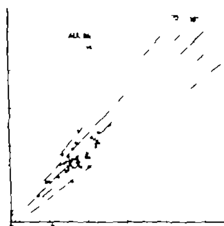


Fig. 5. Comparison of cardiac indices during atrial and sequential pacing.

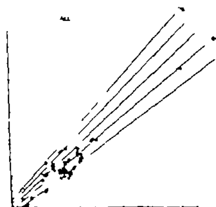


Fig. 6. Comparison of cardiac indices during ventricular and sequential pacing at all three groups of heart rates.

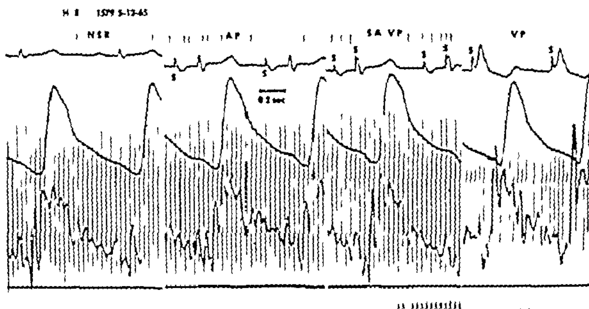



Fig. 7. Various types of pacing technique employed in the study. S refers to the stimulus applied to the atrial or ventricular bipolar electrode catheter or to both catheters.

after the institution of a given pacing rate.

Further statistical analyses are of interest. For all ranges of heart rate there was no difference for the difference between atrial and ventricular pacing between the cor pulmonale and the rheumatic heart disease groups. Similarly, there was no significant difference for the difference between atrial and ventricular pacing between the subjects with cor pulmonale and normal subjects or between the patients with rheumatic heart disease and normal subjects. The data in the normal subjects have been reported previously.[11] Correspondingly, the differences between ventricular and sequential atrioventricular pacing were not different for any of the three groups of patients, i.e., those with cor pulmonale, those with rheumatic heart disease, and normal subjects. The same was true for the differences between the differences for atrial and sequential pacing for the three groups of subjects.

## Discussion

These observations clearly demonstrate that the primary reason for the hemodynamic differences between atrial and ventricular pacing lies in the absence of synchronized atrioventricular activity during ventricular pacing, since the indices during sequential atrioventricular pacing are only slightly less than those during atrial pacing, and the indices during atrial and sequential pacing are generally 20 per cent greater than those during ventricular pacing. Aberrant ventricular depolarization per se results in little decrease in cardiac indices. Part of the small decrement in flow during sequential atrioventricular pacing is probably caused by the shortened P-R interval utilized of necessity in these sequential pacing studies. The artificial P-R interval in these latter studies must be employed to prevent atrioventricular conduction through the normal conduction pathways. It has been clearly shown in this study, and in a related study,[11] that the differences between atrial, ventricular, and sequential atrioventricular pacing are similar for normal subjects and for cardiac patients. The failure of Benchimol and Dimond[7,1] to reach similar conclusions is probably due to the study of fewer patients and internal inconsistencies in their data as previously discussed by us.[11]

**Summary**

Comparison of the effects of atrial, ventricular, and sequential atrioventricular pacing in a group of patients with rheumatic heart disease and in a group with pulmonary emphysema has demonstrated that the absence of synchronized atrioventricular activity rather than aberrant ventricular depolarization is primarily responsible for the hemodynamic difference between atrial and ventricular pacing.

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# The vectorcardiogram recorded with sponge electrodes

*J. Calhoun Witham, M.D.**
*Augusta, Ga.*

Increased use of vectorcardiography has created the dilemma of selecting one lead system from the many that are available. The exclusive adoption of the Frank system seems to be premature, for its practicality does not necessarily compensate for serious theoretical objections. The most disturbing features are the sampling of the electrical field in a single transverse plane and from a small number of points. This design appears to account for the distortions of the X and the Z components revealed by lead fields constructed from torso model experiments.[1] Grid electrodes—which integrate potentials from large areas of the chest—give a significantly better performance.[2-4] Although several such systems have been designed, there are no reports of their being tested clinically on a large scale.

The simplest of the family of grid systems has been suggested by Helm.[5] Large sponge or gauze squares are used as electrodes in the X and Z leads and appear to be acceptable grids. The theoretical foundation depends upon the torso model experiments of Frank.[6] It retains practical advantages of the Frank system, e.g., ease of application and large voltages which minimize interference. It adds others. The care in positioning electrodes and in attaining very low skin resistances at numerous points is not so critical.[6] The construction and maintenance of the input system are simple, since new special electrodes can be cut from sponge or gauze with a pair of scissors and no corrective resistor networks are necessary. Experience suggests that diagnostic features are qualitatively similar but not quantitatively interchangeable with those derived from studies with Frank's system. The following analyses of the sponge VCG in a normal population forms a basis for diagnostic evaluation and should encourage its clinical trial. Whether it will prove to have discriminatory superiority over that of the Frank system or others remains to be seen.

## Patients, recording, measurements

One hundred thirty-three normal Caucasians were selected for this study. The mean age was 24 years. About 90 per cent were hospital personnel. Heart disease was excluded by history, physical examination, x-ray film, hemogram, and electrocardiogram. Cases of bundle branch block of any degree were excluded. ECGs with an r' wave in Lead $V_{3R}$ or Lead $V_1$ caused exclusion as possibly representing minimal right bundle branch block. The age and sex distribution are noted in Table I.

Vectorcardiograms were recorded in the frontal (FP), horizontal (HP), and right sagittal (SP) planes with strips of appropriate scalar X, Y, and Z leads on an Electronics for Medicine recorder. All patients were supine. Anterior and left axillary electrodes were composed of large squares of porous plastic sponge, moist

Received for publication Feb. 3, 1966.
*Professor of Medicine, Division of Cardiology, Department of Medicine, Medical College of Georgia, and Eugene Talmadge Memorial Hospital, Augusta, Ga.

*Table 1 Age and sex distribution of patients*

| Age (yr) | Number (per cent) | Males (per cent) | Females (per cent) |
|---|---|---|---|
| 16–20 | 24 (18) | 4 (17) | 20 (83) |
| 21–25 | 60 (45) | 30 (50) | 30 (50) |
| 26–30 | 35 (26) | 25 (71) | 10 (29) |
| 30–34 | 14 (11) | 5 (36) | 9 (64) |
| Total | 133 (100) | 64 (48) | 69 (52) |

ened with saline A concentrated solution appears to give more consistent results Ordinary limb electrodes were used on the left leg right axilla and a single position on the back [1,7] A suction electrode was used on the neck Since only the QRS loop was to be studied P and T loops were deleted electronically when desirable in order to clarify the initial forces Loops were interrupted at 4 msec intervals The size of the loop was adjusted so that the largest fitted comfortably within the frame loops in all planes were then recorded at this sensitivity A 1 mv calibration was photographed on both channels

Vector loops can be analyzed in numerous ways The scheme followed herein is a modification of that developed by Mexican workers followed by Estes and is an attempt to quantitate morphologic features which have already proved to be diagnostically useful [8] The identification of the major spatial changes in direction allows one to describe most normal records with three vectors each of which has three characteristics—time direction and voltage Time as a descriptive variable is of course lost if used to define the vector itself Loops redrawn from these three vectors more often mimic the distinctive morphology of the original than a similar number of points chosen at arbitrary time intervals The vectors are also consistent with findings in studies of the activation sequence of the normal heart and their major anatomic contributors are mid septum left ventricular free wall and posterobasal left ventricle and septum [14] A recent study indicates that such vectors generally have less variability than those identified at fixed time intervals [13]

Although three vectors are usually adequate to describe normal records they do not always contain sufficient diagnostic information In addition to the three major vectors (Q R and S) three others (20 msec M and S) have been utilized These six plus rotation and time measurements currently constitute a satisfactory system of analysis and are illustrated in Fig 1 They are defined as follows A major directional change is considered to be at least 75 degrees in two or more planes Q is the first major directional change within the first 20 msec R is identified by the maximum leftward extent of the loop S is the first major directional change after the R point Twenty milliseconds is located by timing from the onset of the QRS loop in the plane in which the initial forces are best uncoiled and in other planes by counting backward or forward from previously identified Q or R vector points M is the maximum vector in each plane S is a second major change in direction after the R point and of course the first after the S point as defined above It was identified in the current series in only 15 per cent and data were therefore not tabulated

Spatial voltages were calculated by the use of a special nomogram (Fig 2) The vector angles have been recorded in each plane according to the suggestion of Helm [3] i e in a clockwise manner from 0 to 360 degrees This convention is illustrated in Figs 1 and 3

An IBM 1620 unit was programmed to yield the following information about each of 41 variables mean standard deviation test for normal distribution frequency distribution plot coefficient of variation and coefficient of correlation for each variable against every other The proper

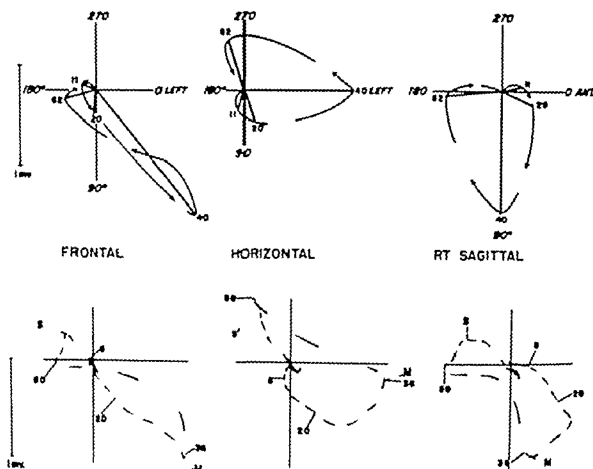



Fig. 3 Top: Loop constructed from mean values of Q, 20 msec, R, and S vectors in Table I. The numbers 11, 20, 40 . . . refer to the average timing (in milliseconds) of these vectors. Heavy lines denote the four vectors. 1 mv standard at extreme left. The convention of angular rotation clockwise from 0 to 360 degrees in each plane is illustrated. Note that the right sagittal view is used and that 0 degree is directly anterior. The frontal plane loop has been drawn to coincide with the most common rotation, i.e., figure-of-eight with counterclockwise efferent limb. *Bottom:* Actual loops illustrating the six most important vectors. Interruptions are at 4 msec intervals and the tail of the comma points in the direction of inscription. On each loop Q, 20, R, and S points are marked by numbers corresponding to their timing from the beginning of the loop—i.e., at *6, 8, 20, 36* and *50* msec, respectively. The maximum (*M*) vector is about 1 msec earlier than R in the frontal and sagittal planes and coincides with it in the horizontal projection. The initial directional change (Q) is sharpest in the frontal plane at 6 msec. It is ill defined in the sagittal plane, where it is identified by timing and its anterior extent as noted on the other two planes. The R point (maximum leftward) is sharply defined on the frontal and horizontal planes and by timing, contour, and vertical displacement on the sagittal. The first sharp break past the R point is at 50 msec, is seen clearly on all planes, and identifies the S vector. The terminal slowing of inscription which begins here is well illustrated. On the lower limb 12 msec past the S point is another final directional change distinct on the frontal and sagittal planes. This fits the definition of the S vector.

ties of each variable were then recalculated for males and females separately and the standard t test was applied to detect significant differences.

**Results**

The angles and voltages in each plane, spatial voltages, and the timing of five vectors are included in Table II. The total duration of the QRS loop, of the segment from the S point to the onset of the T wave (S loop), and of initial superior and anterior forces are noted. Also recorded are measurements of the R and S deflections of the three orthogonal leads and the sum of R in X and S in Z. The means and standard deviations are noted in the conventional manner followed by a range in parentheses.

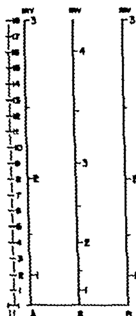



Fig 2 Nomogram to solve the Pythagorean equation $S = \sqrt{X^2 + Y^2 + Z^2}$ where S is the spatial voltage of a given vector and X, Y and Z are the linear voltage expressed on horizontal, vertical and sagittal axes respectively. It is constructed as follows. A scale U of equally spaced units is drawn as a guide (centimeters in the original drawing). The numbers on scale S are square roots of those on scale U, i.e. $S = \sqrt{U}$ where S the number on S and U is the units on U. The numbers on scale A and B are found by the formula $X = \sqrt{U/2}$ and are identical. Calibrations of course may be as detailed as desired. In use any two of the three variables X, Y and Z may be found in one operation—e.g. if one measures the two-dimensional value of a vector in the horizontal plane, both horizontal (X) and sagittal (Z) components will be included. The vertical (Y) contribution to the spatial vector may then be secured from loops in either the frontal or sagittal plane. If these two measurements are then marked on scales A and B and connected with a straight edge, the spatial voltage can be read on scale S.

This is two standard deviations above and below the mean if the distribution was adjudged to be acceptable normal. If not ( ) the range represents 95.5 per cent of the 133 observations obtained by excluding the three highest and three lowest values.

The direction of transcription of the initial limb and the loop as a whole is described in Table III. Table IV presents the 25 statistically significant differences between males and females from the 41 t tests. Table V lists coefficients of correlation and confidence limits of the relationships discussed in the text.

Fig 3 illustrates the frequency distribution of angles and voltages of certain diagnostically important vectors.

## Discussion

*Comparison with Frank system.* Strict comparison is not possible since available data for the Frank system are from various age, sex and racial populations and the methods of measurement are not uniform.[4 5 11 15] An impression may be gained from Fig 4, although it must be remembered that the Frank data are abstracted from three different studies. Apparently the Helm system produces loops which are somewhat more vertically and anteriorly oriented; voltages along the vertical axis (Y) are larger but the posterior extent (Z) is smaller. These differences fit Langner's finding that the Helm Y lead vector is larger than the Frank Y[4] and a comparison of major deflections of the Helm Z with those of Pipberger for the Frank Z, which indicate a dominant posterior deflection for that system.[14] Hugenholtz unfortunately reports only angular measurements but the same trends are apparent.[15] There is no clear choice between the systems in terms of variability of normal values based on the indirect comparisons available.

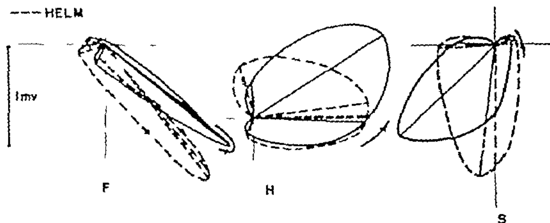
*Characteristics of the normal vectorcardiogram.* The availability of statistical correlations of each variable with every other permits a reasonably objective summary of the interrelationship of the principal vectors. The most useful points are discussed below and are based upon the correlations presented in Table V.

A. INITIAL VECTORS. The Q vector is consistently anterior and usually rightward, but in the frontal plane the positions of Q and R (or maximum) vectors are largely interdependent. The angle between them is consistently wide (mean about 145 degrees). When the maximum vector is horizontal, Q is usually inferior and to the right, and when the maximum vector is vertical, Q becomes superior and often slightly leftward. These relationships generally determine the direction of transcription of the efferent limb in the frontal plane—i.e. counterclockwise (CCW) with

FRONTAL 20 msec | FRONTAL R | HORIZONTAL R

HORIZONTAL S | SAGITTAL Q | SAGITTAL 20 msec

Fig 3 Distribution of angles and voltages of some diagnostically important vectors The centripetal scale in each diagram in millivolts and the angular references follow those of Helm which are illustrated in Fig 1




| Voltage | Orthogonal Leads (mv) Frank | Helm | Voltage | Maximum Vectors (mv) Frank | Helm | Voltage | Spatial (mv) Frank | Helm |
|---|---|---|---|---|---|---|---|---|
| R/S in X | 1.2/3 | 1 1/2 | FP | 1 6 – 4 | 1 7 – 4 | Q | 17 – 09 | 22 ± 13 |
| R/S in Y | 1 0/2 | 1 3/1 | HP | 1 5 ± 4 | 1 1 ± 4 | R | 1 3 – 4 | 1 7 – 5 |
| R/S in Z | 4/9 | 4/5 | SP | 1 3 4 | 1 3 ± 4 | S | 43 – 23 | 60 – 29 |

Fig 4 Superimposed loops for the Frank and Helm systems constructed from mean values The four vectors indicated for each loop in each plane are respectively Q R S and M The source for the first three in the Frank loops is from McCall and for the M vector is an average of those reported by Draper[4] and Brston[16]

*Table II Quantitative data on normal QRS loops—Helm system*

| | Q | 0 msec | R | S | M |
|---|---|---|---|---|---|
| Angles (degrees) | | | | | |
| FI | 198 ± 69 (60–336) | 93 ± 83 (15–300) | 50 ± 14 (24–78) | 164 ± 74 (17–311) | 51 ± 21 (20 80) |
| HP | 108 ± 26 (43–142) | 72 ± 34 (3 –107) | 0 ± 16 (335–30) | 254 ± 24 (225–300) | 354 ± 37 (240–25) |
| SI | 318 ± 37 (295–60) | 24 ± 37 (325–60) | 90 ± 20 (57 116) | 175 ± 33 (109–241) | 97 ± 30 (57 219) |
| Voltage (m ) | | | | | |
| FI | 14 ± 09 (0 30) | 24 ± 17 ( 03– 60) | 1 6 ± 4 ( 7–2 5) | 32 ± 24 ( 05– 90) | 1 7 ± 4 ( 8 2 6) |
| HI | 20 ± 11 ( 12 50) | 34 ± 13 ( 13– 0) | 1 1 ± 4 ( 3 1 9) | 53 ± 26 ( 1–1 1) | 1 1 ± 4 ( 4–1 8) |
| SI | 21 ± 17 ( 12 51) | 35 ± 15 ( 13– 73) | 1 2 ± 4 ( 4–2 1) | 56 ± 28 ( 24 1 2) | 1 3 ± 4 ( 6–2 1) |
| Spatial | 22 ± 13 ( 17 63) | 38 ± 17 ( 13– 78) | 1 7 ± 5 ( 7 2 6) | 60 ± 29 ( 6–1 4) | |
| Timing (msec ) | 11 ± 3 (5–18) | — | 40 ± 5 (32 50) | 62 ± 7 (47 76) | — |

Anterior duration = 41 ± 10 (26–65)
Initial superior duration = 12 ± 8 (0–27)
Total QRS duration = 91 ± 13 (74 113)
S loop duration = 28 ± 9 (14–49)

Voltage in orthogonal lead (mv )

| | | |
|---|---|---|
| X | R = 1 1 ± 4 ( 3 1 9) | S = 17 ± 17 (0– 48) |
| Y | R = 1 3 ± 5 ( 41–2 5) | S = 14 ± 19 (0– 81) |
| Z | R = 41 ± 22 ( 15– 84) | S = 52 ± 26 (0–1 04) |

R + S = 1 6 ± 5 ( 6–2 6)

A C ... deflection
Q 0 ... R S and M (maximum) ... FP HP SP = Frontal horizontal and sagittal plane

*Table III Rotation of efferent limb and QRS loops as a whole 133 cases (per cent)*

| Plane | CW | CCW | Figure of eight/undet |
|---|---|---|---|
| Frontal | | | |
| EFF | 29 | 63 | 8 |
| QRS | 27 | 14 | 59 |
| Horizontal | | | |
| EFF | 0 | 100 | 0 |
| QRS | 0 | 82 | 18 |
| Sagittal | | | |
| EFF | 98 | <1 | <1 |
| QRS | 92 | <1 | |

EFF Efferent limb QRS QRS loop [illegible] CW CCW Clockwise [illegible] counterclockwise [illegible] Rot [illegible] limb undeterminate Figure-of-eight QRS loops with [illegible] crossover

horizontal loops and clockwise (CW) with vertical ones (Fig 5)

The 20 msec vector is also normally anterior and usually inferior Its distribution in the frontal and sagittal planes is seen in Fig 3 The few superiorly oriented vectors with the highest voltages are from vertically oriented loops with CW efferent limbs The maximum durations of initial superior forces were also seen in vertically oriented loops

The rotation of the efferent limb of the loop is consistent in the horizontal plane (CCW) and in the sagittal plane (CW) (Table III) Spatial voltages of all vectors S excepted seem to vary together i e with high voltage Q and 20 msec vectors R and maximum vectors also tend to be large The voltage of all vectors is also directly related to the timing For example Q vectors of longer duration are generally found in loops with later R and S points and larger total QRS times such loops tend to have higher voltages

*Table IV Differences in values between sexes*

| | Variable | | Males (Mean ± S E) | Females (Mean ± S E) | t | p < |
|---|---|---|---|---|---|---|
| Time (msec) | Q vector | | 12 14 ± 44 | 10 75 ± 30 | −2 620 | 01 |
| | R vector | | 42 31 ± 56 | 38 47 ± 52 | −4 985 | 001 |
| | S vector | | 64 57 ± 94 | 58 73 ± 65 | −5 174 | 001 |
| | Total QRS | | 94 54 ± 1 22 | 86 76 ± 1 65 | −3 725 | 001 |
| Angle (degrees) | 20 msec vector FP | | 125 30 ± 12 10 | 63 7 ± 7 04 | 4 477 | 001 |
| | R vector FI | | 43 43 ± 1 84 | 55 07 ± 1 22 | 5 311 | 001 |
| | M vector FI | | 43 51 ± 3 05 | 58 18 ± 1 53 | 4 381 | 001 |
| | 20 msec vector SI | | 11 56 ± 3 06 | 34 85 ± 5 19 | 3 802 | 001 |
| Voltage (mv) | Q vector | FI | 16 ± 013 | 12 ± 008 | −2 709 | 01 |
| | | HP | 22 ± 014 | 18 ± 012 | −2 254 | 05 |
| | | SI | 24 ± 016 | 18 ± 010 | −3 251 | 01 |
| | | Spatial | 25 ± 018 | 19 ± 012 | −2 849 | 01 |
| | R vector | FI | 1 79 ± 054 | 1 46 ± 047 | −4 525 | 001 |
| | | HI | 1 30 ± 046 | 86 ± 034 | 7 686 | 001 |
| | | Spatial | 1 83 ± 056 | 1 48 ± 050 | −4 651 | 001 |
| | M vector | FI | 1 83 ± 058 | 1 53 ± 045 | −4 217 | 001 |
| | | HI | 1 31 ± 043 | 90 ± 030 | −7 691 | 001 |
| | S vector | HI | 60 ± 031 | 47 ± 029 | −2 981 | 01 |
| | | SI | 67 ± 035 | 50 ± 032 | −2 44 | 01 |
| | | Spatial | 66 ± 036 | 54 ± 035 | −2 360 | 05 |
| | Orthogonal lead voltages | R | 1 31 ± 050 | 86 ± 036 | −7 319 | 001 |
| | | $S_y$ | 18 ± 031 | 10 ± 015 | −2 360 | 05 |
| | | R | 47 ± 032 | 34 ± 019 | −3 596 | 001 |
| | | S | 57 ± 033 | 46 ± 028 | −3 010 | 01 |
| | | R + S | 1 90 ± 055 | 1 31 ± 041 | −8 487 | 001 |

*Table V Statistical basis for correlations cited in description of normal loops*

| | Variable | versus Variable | | p < |
|---|---|---|---|---|
| Initial vector | Q angle—FP | R angle—FP | 44 | 001 |
| | Q angle—FP | M angle—FP | 37 | 001 |
| | Q voltage—Spatial | R voltage—Spatial | 48 | 001 |
| | Q voltage—Spatial | 20 voltage—Spatial | 44 | 001 |
| | Q time | I time | 47 | 001 |
| | Q time | S time | 42 | 001 |
| | Q time | Total QRS time | 26 | 01 |
| Mid loop vectors | R angle—FP | M angle—FP | 72 | 001 |
| | R angle—HP | M angle—HP | 9 | 001 |
| | R angle—SP | M angle—SP | 47 | 001 |
| | R angle—FP | R voltage—HP | − 57 | 001 |
| | R time | R voltage—Spatial | 51 | 001 |
| | R + S voltage | M voltage—FP | 59 | 001 |
| | R + S voltage | R voltage—Spatial | 64 | 001 |
| Terminal vector | S loop duration | Total QRS time | 5 | 001 |
| | S time | Total QRS time | 35 | 001 |
| | S voltage—Spatial | Total QRS time | 24 | 01 |
| | S voltage—Spatial | S loop duration | 54 | 001 |

When n = 133
r = 22
m = 28

M Max... vector ... 20-msec ... FP HP SP Frontal ... horizontal and ... planes ... T ... QRS ... 8 ...

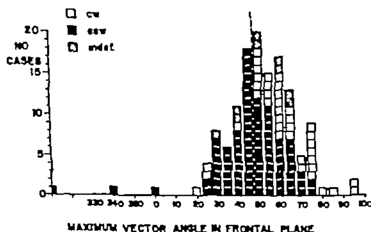



Fig. 5 Relation of the maximum vector ∠FP to rotation of the Q20 segment in the frontal plane. The Q20 segment refers to the efferent limb as far as the R point. The incidence of clockwise rotation increases as the maximum vector moves to the right. The vertical dotted line indicates the best point of separation (4 degrees). To its left only 8 per cent of the efferent limbs are clockwise but to its right 45 per cent are. The shaded squares (indet) represent limbs whose rotation was not clearly clockwise (CW) or counterclockwise (CCW).

B MID LOOP VECTORS The distribution of R vector angles is narrow in all planes and usually in close agreement with the M vector angle in the frontal and horizontal planes An exception is with vertically oriented loops where the M vector is to the right of R in the frontal plane The agreement is also less close in the sagittal plane where the maximum vector is frequently posterior to R There is no valid correlation between the axes of the maximum or R vectors in the frontal plane and their counterparts in the horizontal plane The voltages of mid loop vectors in the horizontal plane are of course greatly influenced by the spatial orientation of the loop If it is elongated along the vertical axis it usually presents a smaller image in the horizontal plane

Two VCG counterparts of ECG criteria for left ventricular hypertrophy are worthy of comment The time of the R vector (counterpart of the intrinsicoid deflection) generally correlates with the spatial R vector voltage The voltage sum R + S (counterpart of $R_{V5} + S_{V1}$) also correlates with the spatial voltage of R and with the largest M vector (frontal plane)

In view of attempts to diagnose posterior infarctions from the extent or duration of anterior forces the wide range of both are noteworthy

C TERMINAL VECTORS The last portions of the normal heart to be depolarized are probably the posterobasal portions of the left ventricle and septum [18] The direction of the S vector fits this site well An obvious characteristic of most normal loops is the terminal slowing beginning near the S point which undoubtedly contributes to the change in direction which allows its identification This presumably reflects a physiologic slowing of excitation possibly due to a paucity of Purkinje fibers in this area [18] Its duration is highly variable and is apparently the largest single factor in determining the duration of the QRS loop (Fig 6) Its duration is also closely related to the voltage of the S vector When delay is pronounced the S vector may be the largest in the horizontal and sagittal planes

It is apparent from Fig 3 that a more precise evaluation of some vectors may be obtained by considering the interdependency of angle and voltage For example an S voltage of 1 0 mv and an angle of 230 degrees in the horizontal plane are within normal ranges but the combination

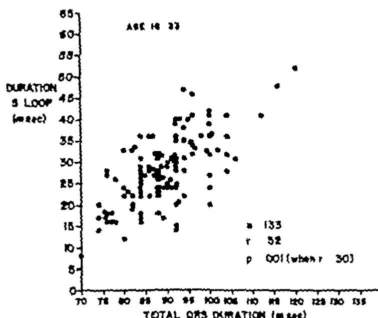



Fig 6 Relation of duration of S loop to that of the QRS complex The S loop is the segment from the S point to the beginning of the T loop (Fig 1) Total QRS duration was plotted against 40 measured variables but this was by far the most significant correlation

is not Voltages of this magnitude are usually seen only with more directly posterior S vectors i e 255 to 275 degrees This is a crude illustration of the largely unexplored potential of multidimensional analysis[18]

A final sharp change in direction noted in 15 per cent of records has been called the S point identifying the S vector It is slightly superior to S closer to the null point by 8 to 24 msec and its spatial voltage is less In the horizontal plane it is frequently indistinct being slightly to the right or left of the S vector S vectors without these characteristics have been tentatively considered to be abnormal usually indicating either right ventricular hypertrophy or bundle branch block

D ROTATIONAL CHARACTERISTICS In the frontal plane most loops are complex and seen on edge (Table III) Generally open loops with simple rotations have maximum vectors near the horizontal (CCW) or vertical (CW) The efferent limb however is usually CCW but its rotation is closely related to the position of the maximum vector in the frontal plane (Fig 5)

In the horizontal plane the efferent limb was universally CCW but 16 per cent (24 cases) showed some later crossing Most commonly this was minimal and at the S point (12 cases) or R point (1 case) where direction changes abruptly The duration of the secondary loop in these 13 cases never exceeded 14 msec Three other cases had open vertically oriented loops with M vectors in the frontal and sagittal planes of 85 ± 10 degrees and as one might expect small on edge loops with major crossings in the horizontal plane One patient had unique narrow on edge loops with major crossovers in all three planes Of particular interest were seven additional patients who had major secondary loops of 16 to 46 msec duration involving the S point The S vector was unusually rightward (220 to 260 degrees in the horizontal plane) and was followed by a prominent S vector Crossover was posterior to the null point These patients may well have had a minor grade of right bundle branch block although the ECG was unconvincing

In the sagittal plane only two cases did not have clearly CW efferent limbs In both the whole loop was CCW due to normal Q and S vector directions associated with unusually high R vectors The ECG revealed left axis deviation In six cases there were brief secondary loops in the sagittal plane (less than 16 msec) involving the Q (1 case) R (3 cases) and S (2 cases) points The previously mentioned patient with on edge loops in all planes was an additional unusual variant case

E DIFFERENCES BY SEX Since sex distribution was approximately equal in this series normal values were recomputed for males and females Table IV lists the statistically significant differences Numerous values for voltage were higher in the male as previously reported[8] It is not surprising therefore that QRS duration and the timing of the major vectors also differ since these are closely related to voltages (Table V) Also the R and maximum vectors in the frontal plane were more rightward in the females and there were accompanying differences in distribution of the 20 msec vector along the vertical axis (frontal and sagittal planes) The differences however are unlikely to be due to sex alone since the groups could not be matched to equalize numerous other variables such as age weight etc

## Summary

A series of 133 normal young adults has been studied vectorcardiographically by the Helm lead system utilizing sponge electrodes A quantitative system of analysis based principally upon loop morphology was used to describe the loops Planar and spatial characteristics of five selected vectors time intervals rotation and major components of the scalar orthogonal leads are recorded Measurements of diagnostic importance are stressed A comparison has been made with data reported for the Frank system In general there was similarity between planar angles for early and late vectors The Helm mid loop vectors however appear to be more rightward and less posterior vertically oriented vectors have higher voltages and posterior ones have lower voltages Males had significantly higher voltages and more horizontal loops than did the females The features of normal loops by this system of reco

and their common variations are described in detail

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# The rheologic properties of low molecular weight dextrans: Fact or fancy?

*G. M. Collins, B.Sc., M.B., B.S., F.R.C.S.*
*J. Ludbrook, B.Med.Sc., Ch.M., F.R.C.S., F.R.A.C.S.*
*Sydney, Australia*

During the past 15 years an extraordinary range of properties has been attributed to low molecular weight dextrans (LMWD). This has resulted in their prescription for an equally wide range of clinical disorders in man.[4] We have had occasion to scrutinize the scientific evidence pertaining to some of the properties claimed for LMWD. A full critique would occupy a moderate sized monograph. We have contented ourselves with presenting an abbreviated but fairly fully documented review. Each section is headed by a commonly believed proposition which is then examined.

*LMWD lowers blood viscosity*

FOR. After burns or crushing injuries in man and animals it has been shown that blood viscosity at all shear rates is raised and that treatment which includes the infusion of LMWD restores the viscosity toward the original value.[11]

AGAINST. The fall in blood viscosity has always been associated with a reduction in hematocrit,[11, 17] which in itself is known to reduce viscosity. Conventional 10 per cent preparations of LMWD have a relative viscosity considerably greater than that of plasma (unpublished observations) in almost all circumstances excepting plasma from patients with multiple myeloma[14]—in other words, it is inherently improbable that LMWD will have a specific viscosity lowering effect on whole blood. Indeed, in studies in which LMWD has been added to blood in vitro, provided that hematocrit is maintained constant or a correction is made for hemodilution, all dextrans of molecular weight greater than 10 to 15,000 have regularly *increased* blood viscosity at all shear rates. Present evidence, therefore, suggests that if viscosity is lowered by adding LMWD to blood in vivo or in vitro, it is because of simple hemodilution rather than from any intrinsic property of the dextran.

*LMWD inhibits the aggregation of red cells in vitro*

FOR. LMWD can diminish the high sedimentation rate of abnormal blood in proportion to the amount added, whether it is added in vivo or in vitro. It increases the electronegative charge on the surface of red cells and by implication increases their mutual repulsion.[4]

AGAINST. No completely satisfactory objective measure of red cell aggregation has yet been evolved. The best available is probably the in vitro sedimentation rate, but this is markedly affected by many factors which include plasma viscosity and specific gravity. Indeed, high molecular weight dextrans or gum acacia in high concentration can produce a very low sedimentation rate even though marked

From the School of Surgery, University of New South Wales, Sydney, Australia.
Received for publication Feb. 21, 1966.

red cell aggregation is visible microscopically.[34] Since 10 per cent LMWD also increases plasma viscosity and specific gravity, it may well be that it lowers sedimentation rate for this reason rather than by a specific disaggregating action. A clear-cut association between the surface charge on red cells and their state of aggregation has not been demonstrated, for both high and low molecular weight dextrans render red cells more electronegative.[8,18] In man, blood with a high sedimentation rate is often associated with a high fibrinogen concentration in the plasma.[34,37,38] It appears that LMWD combines with this substance and indeed may visibly precipitate it;[8,38] plasma fibrinogen content may be much reduced by the addition of LMWD.[38] In much of this work it has been assumed, rather than demonstrated, that the reduction of sedimentation rate by LMWD is associated with physical disaggregation of red cells. Indeed, microscopic examination has shown that this may not be so.[34]

*LMWD prevents sludging of blood in vivo*

FOR. The term "sludging" originated in the motor oil industry,[34] and when applied to blood conjures up a vision of a sticky sediment of red cells obstructing the flow of blood. In disease states, both gravitational separation of the red cells and plasma[39] and the apparent obstruction of small vessels by cellular aggregates[17,32] have been observed to accompany a slowing of blood flow.[37] It is further suggested that these aggregates provide a physical obstruction to blood flow leading to anoxic damage and death.[31,33,37,40,41]

LMWD has acquired a reputation as a flow-promoting agent from reports of its ability to reverse sludging and its sequelae when these have been induced by thermal and mechanical trauma or by the infusion of high viscous dextran.[8,31,33,37,39,40,41] This antisludging property of LMWD is usually equated with its apparent disaggregating effect in vitro.

AGAINST. The pathologic significance of sludging itself is in some doubt.[34]

There is considerable evidence to show that sludging occurs in healthy individuals either spontaneously or after the circulation has been slowed by vasoconstrictor agents or vascular obstruction and that the process is completely and rapidly reversible.[31,34,4,31,4,44,32,4]

There is a lack of consistency in the degree of sludging observed among vascular beds and among different vessels in the same tissue.[7,17,4,34] In a more carefully controlled study, the degree of sludging was not well correlated with the magnitude of the sedimentation rate, nor was LMWD superior to solutions of dextrose or of conventional dextrans in reducing it.[2]

Observations on the bulbar conjunctiva, the region in which most human studies have been carried out, take no account of the normal drainage of aqueous humor into conjunctival veins.[2] This might well create the impression of a separation of red cells from plasma.

Finally and most importantly, it is not clear whether red cell sludging is the initiating factor[17,31,37] in low blood flow states rather than the converse.[4,44] It is entirely possible, therefore, that an apparent "de-sludging" action of LMWD is an indirect result of blood volume expansion and a direct result of the consequent changes in arterial pressure and vascular smooth muscle tone (q.v.).

*LMWD promotes blood flow in small vessels*

FOR. The evidence is difficult to present briefly and difficult to dissociate from that which supports the "de-sludging" action of LMWD. Intravenous infusions of LMWD have been shown to increase blood flow in the forearm in both normal and abnormal human subjects.[32] Blood flow in the dog hind limb has been measured before and after the loss of blood and LMWD has been shown to be superior in restoring blood flow by comparison with isotonic saline or the lost blood itself.[41] In perfused dogs' livers the reduction in flow caused by the addition of high molecular weight dextran has been partly reversed by the further addition of LMWD.[39]

It is reported that the infusion of LMWD in postoperative shocked patients, when compared with the infusion of equal volumes of whole blood, causes a greater increase in central blood volume, central venous pressure, and cardiac output with a lower peripheral resistance.[3] It is sug-

gested that this is due to an effective reduction in blood viscosity in small vessels

AGAINST Blood flow in the human forearm is strikingly increased by a rise in central venous pressure as a reflex response[17,18] and LMWD is a potent short term blood volume increasing agent (q v ) The greater magnitude of this latter action of LMWD by comparison with whole blood or isotonic saline may account for its superiority in restoring blood flow in the dog hind limb Its effect on blood flow in the liver may be one of hemodilution blood plasma was not used as a control

The reported superiority of LMWD as a flow promoting agent in shocked patients neglects its greater blood volume expanding effect by comparison with the control infusions The greater rise in central venous pressure and central blood volume would be expected to cause a reflex reduction in tone in muscle resistance vessels[17,18] the fall in peripheral resistance can be explained in this way rather than by a lowering of viscosity Indeed in a similar study of LMWD in normal and postoperative subjects it is concluded that LMWD has the same hemodynamic action as other blood volume expanders[22] This has been confirmed by the demonstration of an identity of effect of LMWD and conventional dextran in patients with severe arterial insufficiency in the lower limbs[23]

*LMWD acts as a blood volume expander*

FOR When LMWD is infused as a 10 per cent solution it appears that a disproportionately great expansion of blood volume occurs i e the increase in blood volume is 50 to 100 per cent greater than the volume of LMWD infused[23] presumably because of an oncotic effect Its chief advantage as a blood volume expander is that it is cheaper and can be more readily available than whole blood plasma or albumin and it avoids the gross aggregation of red cells which dextrans of higher molecular weight cause

AGAINST The rapid renal excretion of the smaller molecules restores blood volume to control levels within 3 to 6 hours after a single infusion of LMWD[23] although this by no means renders it valueless However the commercial preparations of LMWD contain a proportion of dextrans of molecular weight 70 to 80 000[33] These are destroyed only very slowly probably by metabolic pathways[34] Thus large or long continued infusions of LMWD should result in an ever increasing plasma concentration of those fractions with the very adverse properties which LMWD was designed to avoid[1,2]

*LMWD acts as an osmotic diuretic*

FOR The smaller molecules in LMWD are rapidly excreted by the kidney In normal man 70 to 80 per cent of the fractions below 40 000 mean molecular weight can be recovered from the urine within 12 hours[1,36]

AGAINST A careful study in dogs shows that although LMWD may be excreted in extremely concentrated form (up to 50 per cent) it has a minimal osmotic diuretic action in conventional dosage[35] Indeed the resultant viscosity of the urine may be such as to limit the flow of urine through the renal tubules

## Summary

We are forced to the conclusion that none of the new and extraordinary rheologic properties which have sometimes been claimed for low molecular weight dextrans have yet been proved to be genuine However it does seem that they are comparatively safe short term blood volume expanders

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# An evaluation of computed stroke volume in man

*William B Jones M D**
*Richard O Russell Jr M D*
*Dallas H Dalton Jr M D*
*Birmingham Ala*

A method of obtaining an approximation of the aortic blood velocity from the aortic pressure pulse has been previously reported from this laboratory [1,2] The method consists of obtaining a continuous solution of a simplification of the Navier Stokes equation (the general equation describing fluid dynamics) using the aortic pressure pulse as the input signal to an analogue circuit The simplified equation is as follows

$$\partial P/\partial t \quad 1/s = \rho \frac{du}{dt} + au \qquad (1)$$

P is aortic pressure $t$ is time $\rho$ is a constant for density $s$ is a constant for the rate of pulse transmission $u$ is the blood velocity and $a$ is a blood friction constant The general method has been previously discussed by the authors and others [1-3]

Reasonable validation has been established in dogs by comparison of the derived velocity curves with curves obtained from an electromagnetic flowmeter [2] The previous comparison revealed a correlation coefficient of 0 93 when the two independent flow curves were used as estimates of stroke volume

The method would appear to have its major usefulness in studies of human cardiovascular dynamics Since several assumptions and simplifications are involved in the method further validation of the technique as applied to man is indicated This paper reports a comparison of cardiac outputs derived from the computed aortic velocity curves and results obtained by other methods i e dye dilution and Fick determinations

## Methods

The comparison data were obtained from two studies recently completed in the cardiac catheterization laboratory The first was a study on normal volunteers to determine the effect of eating on hemodynamics at rest and exercise This has been previously reported [4] Ten subjects were studied in this group For each study multiple determinations of cardiac output were obtained by the dye dilution technique with indocyanine green The derived flow curves were recorded simultaneously as will be outlined below

Other data were obtained from exercise studies on 32 patients with known or suspected heart disease This was done as part of a hemodynamic and anatomic evaluation In these patients a resting Fick determination was made Then each subject exercised for 4 minutes and a repeat determination was made during the fourth minute

From the Department of Medicine Medical College of Alabama and the Medical Service Veterans Administration Hospital Birmingham Ala
This study was aided by Grant HDO 4333-05 from the National Institutes of Health
Received for publication March 1 1966
Address Medical College of Alabama 1919 Seventh Ave South Birmingham Ala 35233

In all subjects a No. 5 Teflon catheter was introduced into a brachial artery by the percutaneous technique and advanced until the tip was in the ascending aorta. The pressure was sensed with a Statham P23D manometer. The catheters were optimally damped with a mechanical compression device. The catheter manometer system has been found to be linear to 25 cycles per second.

A multichannel oscilloscopic recorder was used.* The first time derivative of the aortic pressure pulse was obtained with a simple R-C differentiating circuit. The output from this circuit was modified by a computer circuit designed to give a continuous solution of the modified Navier-Stokes equation. The computer circuit used is similar to that previously described by Fry and co-workers.[3] The output from this circuit is considered to have an output proportional to the velocity of flow in the ascending aorta and is recorded as a velocity curve. In addition, a continuous integration of the velocity curve was obtained by means of a recycling integrator which triggers from the R wave of the electrocardiogram.[4] The original aortic pressure signal and its various modifications are illustrated in Fig. 1.

The computer circuit used has a variable adjustment to compensate for variations in inertia and friction. Prior to each study this adjustment was set so that the derived velocity tracing returned to its base line synchronously with the aortic incisura. Once this setting had been made a tracing was obtained prior to and immediately after a determination of cardiac output by either the Fick or the dye-dilution method. No changes in the setting were made during the course of the study.

The assumption is made that the size of the ascending aorta is relatively constant so that the velocity curve obtained in this area would have the same shape as a volume flow curve. Therefore, the height at the end of systole of the integrated velocity curve was measured and considered to be proportional to stroke volume. Such curves were obtained before and after each determination of cardiac output by the Fick or the dye-dilution method. An average figure from at least five cycles

*Electronics for Medicine, Inc., White Plains, N. Y.

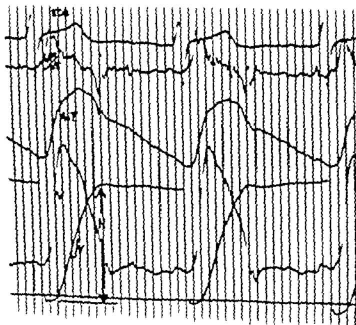



Fig. 1. A representative tracing showing the ECG, the first time derivative of the aortic pressure, the aortic pressure, the blood velocity curve (V) and the integral of the velocity curve (∫V). The measurement H is taken as being proportional to stroke volume.

was obtained in each situation For the initial resting determinations the average figure obtained from the integrated velocity curve was multiplied by heart rate to obtain a figure proportional to cardiac output The determined cardiac output was divided by this figure to provide a calibration constant Subsequent comparison points were obtained by multiplying the heart rate by the average height of the integrated velocity curve by the calibration constant

In the physiologic studies to determine the effect of meals the subject exercised twice and at least one and occasionally two dye dilution outputs were determined during each period of exercise In addition several comparison points were obtainable during the rest period between the two exercise studies For the clinical studies one resting determination was made and one exercise determination

**Results**

A total of 73 comparison points has been obtained 42 from the 10 subjects in the study concerning the effect of meals and 31 from 31 patients undergoing exercises as part of catheterization These ranged from essentially normal subjects to patients with severe mitral aortic or myocardial disease Patients with severe aortic insufficiency or with shunts were excluded The patients with aortic insufficiency were excluded because of the difficulty in assessing the backflow by means of the velocity curves Patients with shunts were excluded because of the difficulties in determining cardiac outputs by either the dye dilutions or the Fick technique The patient studies are consecutive Five subjects were excluded from the tabulation because of inability to duplicate Van Slyke analysis or failure to follow the exercise protocol

Fig 2 is a plot of the cardiac output determined from the derived velocity curves against Fick or dye dilution outputs A correlation coefficient of 0 90 is obtained The regression line is described by $Y = -1.09 + 1.23x$ The standard deviation is 1 85 L per minute As can be seen the scatter is more apparent at the higher output levels

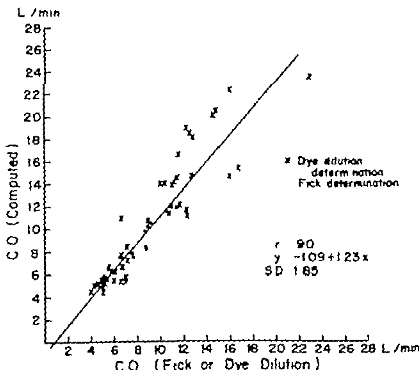



Fig 2 A comparison of cardiac outputs as determined by dye-dilution or Fick method with that computed from velocity tracings obtained by the time derivative method

When the points of comparison with the dye dilution outputs alone are considered the correlation coefficient is 0.92. It is 0.88 for the Fick determinations alone.

**Discussion**

The findings in man are in agreement with those previously made in dogs and confirm that the method of obtaining an approximation of the aortic blood velocity appears to be acceptably accurate. The method exaggerates the stroke volumes at the higher levels, giving a regression line with a steeper slope than the identity line. This can be corrected to some extent by using the regression equation to modify the derived cardiac output.

From Fig. 2 it is apparent that there is moderate scatter, particularly at the higher cardiac outputs. Part of this scatter can be attributed to inaccuracies of the Fick and dye dilution techniques during exercise. In addition, an error in the initial cardiac output determination used for calibration would result in a consistent error in all subsequent computed values. The average percentage of error is essentially constant for all cardiac outputs measured.

The major theoretical assumption in the use of the time derivative is that the rate of pulse transmission ($s$ in Equation 1) is the same for all relevant frequencies in the ascending aorta. If this is assumed, then the time derivative and the spatial derivative of pressure have the same form and $s$ serves as a calibration factor. No direct measurements referable to this have been made in the ascending aorta. However, available evidence suggests that flow impedance varies only minimally with frequency in the ascending aorta.[7,8] By extension, this suggests that $s$ is relatively constant in this area.

Greenfield and Fry recently reported a surprising validation of the time deriva-

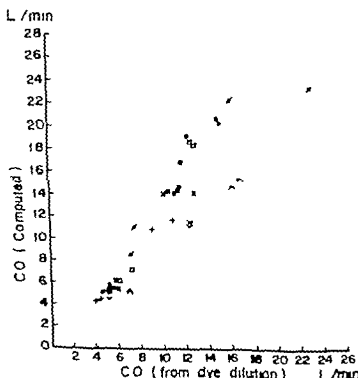



Fig. 3. A display of the comparison of cardiac outputs determined by dye dilution with that computed from the derived velocity tracing [illegible] subjects who had multiple determinations at rest and during exercise. The comparison points from single individuals are differentiated by symbol. Calibration of the computed [illegible] in each individual was obtained from an initial cardiac output value. The calibration [illegible] are not plotted [illegible] graph.

tive technique in the descending aorta They confirm the empirical usefulness of the method but challenge the theoretical assumptions on the basis of discrepancies between the experimental time constant (the ratio of resistance and inductance terms) and the predicted time constant These discrepancies are not surprising in the descending aorta where the flow impedance has been amply demonstrated to be frequency dependent[14] However their conclusions are not necessarily applicable to the ascending aorta In any case the usefulness of the method is determined by experimental validation irrespective of theoretical background

In application it would appear to be preferable in all studies to obtain periodic determinations of output by either the dye or Fick method so as to construct an individual regression line in each subject This would permit a beat by beat study of output and provide detail of the changes in cardiac output determinations obtained by the standard methods All comparison points exclusive of the initial one used for calibration are shown from the subjects in whom multiple determinations were made (Fig 3) *The subjects are identified* by symbol It can be seen that the correlation in each individual subject is better than that of all subjects considered together

It is apparent that the change in the heart rate during exercise is a major determinant of exercising cardiac index In most subjects the stroke volume changes very little with exercise so that the major variable is heart rate Therefore it is conceivable that the correlation coefficient of 0 90 as reported is primarily a correlation of heart rate and cardiac output To test this hypothesis it was assumed that the resting stroke volume was a constant and that all subsequent variation was due to change in heart rate The correlation of Fick or dye cardiac output with an output approximation from heart rate multiplied by resting stroke volume is 0 74 It is apparent that stroke volume as determined by the method reported in this paper improves the correlation considerably

The technique appears to have considerable potential as an adjunct to the standard methods of determining cardiac output in that it permits assessment of beat by beat changes and rapid changes It has the advantage of requiring only a single lumen catheter in the ascending aorta However accurately obtained properly damped aortic pressure curves are a necessity if valid curves are to be secured

## Summary

Data for validation in man of a method for determining continuous cardiac output are presented Seventy three points of comparison between a Fick or dye dilution value and a value computed from the pressure pulse in the ascending aorta give a correlation coefficient of 0 90 The method described is based on a continuous solution of the Navier Stokes equation with the first time derivative of the aortic pressure used as the input signal

We wish to express appreciation to Dr Donald A McDonald for criticism and advice

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# Five-year follow-up study of cases suggestive of acute myocarditis

*Elias Bengtsson M D **
*Berndt Lamberger M D*
*Stockholm Sweden*

The findings in various autopsy series[26-37] indicate that acute myocarditis frequently attends acute infectious diseases In clinical practice however the diagnosis is more rare The diagnostic criteria often based solely upon electrocardiographic findings are not always unequivocal In earlier investigations[3-19] of normal individuals and individuals suspected of having acute myocarditis an attempt was made to enhance the electrocardiographic diagnosis coordinate various clinical findings determine the physical working capacity as a function of the stroke volume of the heart and apply a more fully developed method for determination of the heart volume According to the criteria applied in these investigations the physical working capacity of patients with myocarditis was reduced to some extent the reduction being particularly conspicuous in relation to heart volume which was frequently enlarged

The prognosis of acute myocarditis has always been regarded as being favorable (except in cases of diphtheria and trypanosomiasis) although no major series has been followed over long periods In order to shed further light on this problem we followed for 5 years after the onset a number of patients from the previous series of cases of acute myocarditis The findings were compared with those for cases in which the diagnosis of myocarditis had been doubtful and with those obtained in a control series which 5 years earlier had shown no signs of cardiac involvement Examinations and methods were the same as before

## Material

During the period 1950 through 1955 a large number of patients suffering from acute infectious diseases was examined electrocardiographically with standard leads usually at intervals of 1 week As a rule both chest and unipolar extremity leads were taken whenever the standard leads revealed manifest or suspected changes Thus 2 310 patients were examined with chest leads In most cases pathologic changes were attributed to extracardiac causes but in 201 cases they were considered to be suggestive of acute myocarditis The latter cases were subjected to electrocardiographic and other studies which along with the principles of selection have already been reported

Briefly summarized the repeated electrocardiographic examinations did not reveal stationary changes and the changes were not attributed to tachycardia congenital or previously acquired heart dis-

F[illegible] C[illegible] Hospital Stockholm Sweden.
This study was aided by grant from [illegible] Council [illegible]
Received for publication March 14 1966
[illegible] Stockholm [illegible] Sweden

case or cardiosclerosis. Discarded were cases in which the ECG changes could be duplicated or eliminated by certain agents with a neurovegetative action, as well as cases with concomitant electrolyte disturbances and those in which certain other extracardiac factors might have influenced the ECG. Also excluded were cases with certain transient disturbances of rhythm and conduction not associated with other electrocardiographic changes or other clinical symptoms.

It was planned to follow up during the years 1955 through 1959 those patients who had been hospitalized during the period 1950-1954. This series totaled 130 cases. Excluded from the follow-up investigation, however, were all patients over the age of 49, patients with paralysis, 15 patients who had moved from Stockholm, and 5 who could not be traced. No other selection was practiced, and the follow-up study thus comprised a total of 90 cases which 5 years earlier had been classed as suggestive of acute myocarditis.

The previous investigations had included 61 cases in which the diagnosis of myocarditis was doubtful. Twenty-six of these patients who were under 50 years of age and free of paralysis, but otherwise unselected, underwent follow-up examinations.

In another previous investigation,[9] electrocardiograms (ECG's) had been recorded and the working capacity determined in 63 patients hospitalized for various infectious diseases; the examinations had revealed no signs of cardiac involvement either during hospitalization or after 1 month of convalescence. Thirty-four cases were taken from this series on the same basis as before and used as a follow-up control group.

The present investigation is concerned chiefly with the 90 cases in the first group. At the onset 5 years earlier the primary acute infectious disease in 50 per cent of the cases had been due to hemolytic streptococci. The distribution of diseases in the group is shown in Table I. The subgroup comprising 12 cases of miscellaneous infectious diseases was made up as follows: 2 cases of infectious hepatitis, 2 of bacillary dysentery, 2 of pertussis, 3 of obscure fever, and 1 each of mononucleosis, diphtheria, and measles.

Streptococcal diseases also accounted for 13 (50 per cent) of the 26 dubious

*Table I. Subjective symptoms and phonocardiographic findings in cases suggestive of myocarditis*

| | Total series | | Number of patients with subjective symptoms | Systolic murmurs | | |
|---|---|---|---|---|---|---|
| | Number | Per cent | | High frequency | Pansystolic | Mid-systolic |
| Rheumatic fever | 18 | 20 | 3 | 6 | 2 | 2 |
| Scarlet fever | 20 | 22 | 4 | 8 | 2 | 2 |
| Other streptococcal diseases | 6 | 7 | 0 | 0 | 0 | 0 |
| Nonhemolytic tonsillitis | 9 | 10 | 4 | 2 | 0 | 0 |
| Aseptic meningitis | 16 | 18 | 3 | 1 | 1 | 0 |
| Poliomyelitis | 4 | 4 | 2 | 0 | 0 | 0 |
| Pneumonia | 5 | 6 | 1 | 1 | 1 | 0 |
| Miscellaneous infectious diseases | 12 | 13 | 6 | 1 | 1 | 0 |
| Total number of cases | 90 | | 23 | 19 | 7 | 4 |

cases in the second group including 5 of polyarthritis (but none of rheumatic fever according to Jones criteria) Of the other 13 cases there were 5 of upper respiratory infections and pneumonia 2 of poliomyelitis 2 of aseptic meningitis and 4 of paratyphoid fever Aside from a greater proportion of cases of infectious hepatitis and the absence of rheumatic fever the acute infectious diseases showed much the same distribution in the control group

During the 5 years after the hospitalization no one in these series had been hospitalized for any infectious disease nor seriously ill at home from any similar disease At the time of the follow up examination all were healthy and no one had suffered from any respiratory or other infectious disease of any consequence during the previous 4 weeks

**Methods**

The methods applied for electrocardiographic examination at rest[3] and during exercise[4] and for determination of the physical working capacity and heart volume[4,5] were identical with those used in the investigations 5 years earlier In the orthostatic tests ECGs were recorded after the subjects had been in the erect position for 10 minutes Anamnestic data were annotated in accordance with the previously used questionnaire

Electrocardiograms were recorded from CR leads and during exercise from CH leads (chest head)[4] In the exercise tests ECGs as well as heart rate and respiration rate were recorded at 2 minute intervals The physical working capacity was determined by bicycle ergometer tests at the load coinciding with a heart rate of 170 beats per minute under steady state conditions[11] Heart volume was determined roentgenologically by the method of Kjellberg Lonroth Rudhe and Sjostrand[12,13]

Electrocardiograms were evaluated on the basis of previously reported normal values[14] heart volumes and working capacities on the basis of the regression lines with 95 and 99 per cent limits reported for normal series[5]

**Results**

*Subjective symptoms* (*Table I*) All subjective distress recorded in the following was stated to have arisen at the time of or shortly after hospitalization 5 years earlier

Fatigue was reported without descriptive detail by 9 patients (10 per cent) only 2 of whom mentioned no other symptoms Dyspnea or other physical impairment that could be satisfactorily defined was reported by 12 patients Precordial pain symptoms of oppression or arrhythmia were reported by 18 patients (20 per cent) 6 of whom made no reference to other symptoms

The distribution of symptoms by type of disease is shown in Table I The groups with rheumatic fever scarlet fever and aseptic meningitis had roughly the same incidence of symptoms (approximately 20 per cent) but in the group with miscellaneous diseases every second patient had symptoms of some type

At the time of examination 4 of the patients with subjective distress had sedimentation rates of 20 to 30 mm and in 3 of these 4 the antistreptolysin titers were elevated to 800 500 and 640 units per milliliter None of them however reported any aggravation of the subjective symptoms

Out of the total of 23 patients only 2 exhibited abnormalities on the resting ECGs 7 had electrocardiographic abnormalities on the orthostatic tests including 3 with no other ECG changes The exercise ECGs were abnormal in 10 patients only one of whom had shown abnormalities on the resting ECG

In 8 of the 23 patients the physical working capacity was abnormally low (falling outside the 95 per cent limit) in relation to body weight in 11 it was abnormally low in relation to heart volume In 8 of these patients the values were abnormal in relation to one but not to both of these factors Six patients had a normal working capacity in relation to each of the two factors Heart volume was abnormally large in relation to body weight in 7 patients but normal in 16

*Phonocardiographic findings* (*Table I*) The physical findings were consistent with the phonocardiographic data Analysis of phonocardiograms from the entire series revealed not a single patient with diastolic murmurs such murmurs as were noted

were largely referable to the groups with rheumatic fever and scarlet fever. The other groups included only occasional cases of murmurs. The incidences were approximately equal —about 60 per cent— for the rheumatic fever and the scarlet fever groups.

As for systolic murmurs, only the high frequency, the pansystolic, and the mid systolic were recorded. In the total series the respective incidences of these murmurs were 21.1, 7.8, and 4.4 per cent. In the combined rheumatic fever and scarlet fever groups, high frequency murmurs were noted in 36.9 per cent, pansystolic and mid systolic murmurs each in 10.5 per cent.

Of the 21 patients with murmurs, 15 had abnormal ECGs, roughly one half had low working capacities, and approximately one fourth had enlarged heart volumes.

*Electrocardiographic findings (Tables II and III).* Abnormalities were noted on the resting ECGs of 21 patients, approximately one half of whom had normal exercise and orthostatic ECGs. Ten patients had abnormal ECGs on the orthostatic test, but in 5 of them the resting and exercise ECGs were normal. Twenty eight showed electrocardiographic abnormalities on the exercise test, but 16 of these had normal ECGs at rest and on the orthostatic test.

The most common abnormalities were those in the terminal segment, disturbances in rhythm being next in order, and conduction disturbances comparatively rare.

Atrioventricular conduction disturbances were observed chiefly in cases of rheumatic fever, as were intraventricular conduction abnormalities. Disturbances in rhythm

*Table II. Distribution of abnormal electrocardiograms*

| *Abnormalities on* | *Number of cases* |
|---|---|
| Resting ECGs | 10 |
| Orthostatic ECGs | 5 |
| Exercise ECGs | 16 |
| Resting + orthostatic ECGs | 0 |
| Resting + exercise ECGs* | 8 |
| Orthostatic + exercise ECGs | 2 |
| Resting + orthostatic + exercise ECGs† | 3 |
| Total number of cases | 44 |

*Working capacity and heart volume undeterminable in 2 patients.
†Working capacity and heart [illegible] undeterminable in 1 patient.

*Table III. Types of electrocardiographic abnormalities in various infectious diseases*

| | | *Rhythm disturbances* | | | *Atrioventricular conduction disturbances* | | | *S-T segment and T wave changes* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Total cases* | *Resting* | *Orthostatic* | *Exercise* | *Resting* | *Orthostatic* | *Exercise* | *Resting* | *Orthostatic* | *Exercise* | *Total abnormalities* |
| Rheumatic fever | 18 | | | | 2 | 1 | 1 | 1 | 1 | 3 | 9 |
| Scarlet fever | 20 | 2 | | 1 | 1 | | | 3 | 3 | | 12 |
| Other streptococcal diseases | 6 | | | | | | | 1 | | 1 | 2 |
| Nonstreptococcal tonsillitis | 9 | | | | | | | 2 | 1 | 2 | 5 |
| Aseptic meningitis | 16 | 1 | | 2 | | | | 4 | 1 | 10 | 18 |
| Poliomyelitis | 4 | 1 | 2 | 2 | | | | 2 | | | 7 |
| Pneumonia | 5 | | | 2 | | | | | | | 2 |
| Miscellaneous infectious diseases | 12 | | | 3 | | | | 2 | 1 | | 6 |
| Number of changes | 90 | 4 | 2 | 10 | 3 | 1 | 1 | 15 | 7 | 18 | |

on the other hand were usually associated with cases of nonstreptococcal disease notably poliomyelitis and pneumonia Abnormalities of the terminal segment were recorded in all disease groups with the highest incidence in cases of aseptic meningitis and the lowest in cases of rheumatic fever

Disturbances in rhythm first evidenced on the exercise ECGs were largely referable to the groups with nonstreptococcal diseases Such abnormalities of the terminal segment as were first manifest on the exercise ECGs were *most commonly* associated with streptococcal diseases but were also noted in a number of cases of aseptic meningitis

Disturbances in rhythm on orthostatic tests were confined to cases of poliomyelitis whereas abnormalities of the S T segment and T wave on such tests were recorded in the majority of other groups although most commonly in cases of scarlet fever

*Abnormal electrocardiograms in relation to reduced working capacity and abnormally large heart volume* Cases in which there was an abnormal ECG were divided into two groups one with a streptococcal etiology and the other with a nonstreptococcal etiology For the streptococcal disease group the working capacity was abnormally low in 5 patients and normal in 8 whereas the heart volume was abnormally large in 2 but normal in 11 For the other group the working capacity was impaired in 12 patients and normal in 11 the heart volume was abnormally large in 6 and normal in 17 Among the patients with aseptic meningitis in the nonstreptococcal group abnormally low and normal working capacities as well as abnormally large and normal heart volumes showed approximately equal distributions (about 5 or 6 cases in each of the categories)

*Electrocardiographic abnormalities at different examinations in relation to working capacity and heart volume (Table IV)* In 17 cases in which the resting ECG was abnormal both the physical working capacity and the heart volume were studied The working capacity evaluated in relation to heart volume was abnormally low in 11 of the 17 patients evaluated in relation to body weight it was abnormally low in 6 and within the normal range in 11 Only 3 of the 17 patients had enlarged heart volumes

In addition to these 17 patients there were 3 in whom right bundle branch block was manifest on the resting ECGs (but not on the exercise ECGs) Each of the 3 had a normal working capacity and heart volume

Of 9 patients with electrocardiographic abnormalities on the orthostatic tests 4 had reduced working capacities and 1 had *an abnormally large heart volume* All patients with abnormal working capacity and/or heart volume were referable to the nonstreptococcal disease group

Of 27 patients with abnormal exercise ECGs 7 had abnormally low working capacities in relation to body weight and 13 in relation to heart volume Nine had abnormally large heart volumes in relation to body weight

*Working capacity (Table V)* Reduced working capacities were no more common in patients with streptococcal diseases than in the others In the total series the physical working capacity —considered in relation to either body weight or heart volume—was reduced to values below the 95 per cent limits in 41 per cent of the patients The working capacity was abnormally low solely in relation to body weight or age in 15 patients solely in relation to heart volume in 12 and in relation to both heart volume and age or body weight in 17

The impairment of working capacity moreover was more pronounced in relation to heart volume than to body weight in the former context 17 of 29 cases fell below the 99 per cent limits in the latter only 8 of 23

Of the 34 patients with low working capacities 20 had abnormal ECGs and 13 had *abnormally large heart volumes*

*Heart volume (Table VI)* Abnormally large heart volumes in relation to body weight were noted in one fifth of the cases Approximately 50 per cent of these cases exceeded the 95 per cent upper limit of the previously determined normal range and the other 50 per cent exceeded the 99 per cent limit Of the latter 50 per cent the majority were cases of rheumatic fever

*Table IV. Working capacity and heart volume in patients with abnormal electrocardiograms*

| Abnormalities of | Number of cases | Working capacity in relation to | | | | Heart volume in relation to body weight | |
|---|---|---|---|---|---|---|---|
| | | Body weight | | Heart volume | | | |
| | | Low | Normal | Low | Normal | Large | Normal |
| Resting ECG | 17 | 6 | 11 | 11 | 6 | 3 | 14 |
| Orthostatic ECG | 9 | 4 | 5 | 4 | 5 | 1 | 8 |
| Exercise ECG | 27 | | 20 | 13 | 14 | 9 | 18 |
| Total | 53 | 17 | 36 | 28 | 25 | 13 | 40 |

*Table V. Working capacity in relation to body weight or age and heart volume in various infectious diseases*

| | Total number of cases | Working capacity in relation to | | | | | | | | Abnormally low working capacity | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Body weight or age | | | | Heart volume | | | | | |
| | | Below | | Normal | Not examined | Below | | Normal | Not examined | Total number of cases | Per cent |
| | | 95 per cent limit | 90 per cent limit | | | 95 per cent limit | 99 per cent limit | | | | |
| Rheumatic fever | 18 | 2 | 1 | 14 | 1 | 0 | 4 | 13 | 1 | 6 | 35 |
| Scarlet fever | 20 | 5 | 1 | 13 | 1 | 4 | 3 | 12 | 1 | 8 | 42 |
| Other streptococcal diseases | 6 | 1 | 1 | 4 | 0 | 0 | 1 | 4 | 1 | 1 | |
| Nonbacterial tonsillitis | 9 | 4 | 0 | 5 | 0 | 3 | 0 | 6 | 0 | 5 | 56 |
| Aseptic meningitis | 16 | 1 | 2 | 13 | 0 | 2 | 4 | 10 | 0 | 6 | 38 |
| Poliomyelitis | 4 | 0 | 1 | 0 | 3 | 0 | 1 | 0 | 3 | 1 | |
| Pneumonia | 5 | 0 | 0 | 5 | 0 | 0 | 0 | 5 | 0 | 0 | 0 |
| Miscellaneous infectious diseases | 12 | 2 | 2 | 7 | 1 | 3 | 4 | 4 | 1 | 7 | 64 |
| Total number of cases | 90 | 15 | 8 | 61 | 6 | 12 | 17 | 54 | 7 | 34 | 41 |

Of the 17 patients with abnormally large heart volumes approximately one half had abnormal ECGs and 13 had abnormally low working capacities.

*Findings in patients with suspected cardiac involvement on admission to hospital (dubious myocarditis group) (Table VII).* At the time of hospitalization 5 years earlier the ECGs of some patients had not been unequivocally abnormal according to the criteria applied[7] and those of others had been interpreted as being dubious. These patients were subjected to identical examinations at the time of the follow up and the findings are recorded in Table VII in which the cases are grouped with re

*Table VI Heart volume in various infectious diseases*

| | Total number of cases | Heart volume in relation to body weight | | | | Abnormally large heart volume | |
|---|---|---|---|---|---|---|---|
| | | Exceeding | | Normal | Not examined | Number of cases | Per cent |
| | | 95 per cent limit | 99 per cent limit | | | | |
| Rheumatic fever | 18 | 1 | 4 | 12 | 1 | 5 | 28 |
| Scarlet fever | 20 | 2 | 0 | 17 | 1 | 2 | 10 |
| Other streptococcal diseases | 6 | 0 | 1 | 3 | 1 | 1 | |
| Nonhemolytic tonsillitis | 9 | 1 | 0 | 8 | 0 | 1 | |
| Aseptic meningitis | 16 | 2 | 3 | 11 | 0 | 5 | 31 |
| Poliomyelitis | 4 | 0 | 0 | 2 | 2 | 0 | |
| Pneumonia | 5 | 1 | 0 | 4 | 0 | 1 | |
| Miscellaneous infectious disease | 12 | 1 | 1 | 10 | 0 | 2 | 17 |
| Total number of cases | 90 | 8 | 9 | 67 | 5 | 17 | 20 |

*Table VII Follow up findings in the dubious cases of myocarditis*

| | Streptococcal diseases (13) | Nonstreptococcal diseases (13) | Total number (26) | Per cent of total number |
|---|---|---|---|---|
| Subjective symptoms | 5 | 2 | 7 | 27 |
| Elevated antistreptolysin titer | 2 | 2 | 4 | 15 |
| Abnormal PCG | 5 | 0 | 5 | 19 |
| Abnormal resting ECG | 1 | 2 | 3 | 12 |
| Abnormal orthostatic ECG | 5 | 2 | 7 | 27 |
| Abnormal exercise ECG | 3 | 4 | 7 | 27 |
| Total number of patients with abnormal ECG | 7 | 6 | 13 | 50 |
| Low working capacity | 8 | 4 | 12 | 46 |
| Enlarged heart volume | 4 | 1 | 5 | 19 |

spect to diseases of streptococcal or other etiology

*Findings in patients with no signs of cardiac involvement on admission to hospital (Control Group)* (*Table VIII*) Of the 34 patients comprising this group 16 had had 5 years earlier infectious diseases due to hemolytic streptococci and 18 had had infectious diseases of other etiology

At follow up examination 2 patients reported subjective symptoms one of them fatigue and the other dyspnea and precordial pain The latter patient was a 16-year old girl who had suffered from scarlet fever Her resting ECG showed partial right bundle branch block the orthostatic ECG certain abnormalities the exercise ECG a diphasic T at 4 minutes after exercise the phonocardiogram a low frequency early systolic murmur of low amplitude and the functional test a working capacity below the 99 per cent limit of a normal series

The second of the two patients with abnormal exercise ECGs exhibited a negative T wave in the apical lead during exercise and an isoelectric T wave in the same lead after exercise This patient a 15 year old boy had a somewhat low blood pressure of 105/60 mm Hg but in all other respects the findings were normal

*Comparison of cases without cases with*

*Table VIII. Incidence of signs and symptoms in three groups examined 5 years earlier: patients without signs of cardiac involvement (controls), patients with dubious myocarditis, and patients with presumptive myocarditis*

| *Follow-up findings* | *Controls (34)* | | *Dubious myocarditis (26)* | | *Presumptive myocarditis (90)* | |
|---|---|---|---|---|---|---|
| | *Number* | *Per cent* | *Number* | *Per cent* | *Number* | *Per cent* |
| Subjective symptoms | 2 | | 7 | 27 | 22 | 24 |
| Elevated antistreptolysin titer and/or E.S.R. | 8 | 23 | 4 | 15 | 25 | 28 |
| Abnormal PCG findings | 1 | | 5 | 19 | 21 | 23 |
| Abnormal resting ECG | 0 | | 3 | 12 | 17 | 19 |
| Abnormal orthostatic ECG | 4 | 12 | 7 | 27 | 9 | 10 |
| Abnormal exercise ECG | 2 | | 7 | 27 | 27 | 30 |
| (Total with ECG changes) | 5 | 14 | 13 | 50 | 44 | 49 |
| Low working capacity | 1 | | 12 | 46 | 34 | 41 |
| Enlarged heart volume | 0 | | 5 | 19 | 17 | 19 |

*suspected, and cases with manifest cardiac involvement 5 years earlier.* For the two groups in which myocardial lesions had been diagnosed or suspected 5 years earlier, the follow-up findings were much the same as before except in regard to the incidence of abnormal ECGs on the orthostatic tests. The group of patients with presumptive myocarditis had the same incidence (approximately 10 per cent) of abnormal orthostatic ECG as did the control group (orthostatic reactions alone were not here regarded as manifestations of cardiac involvement).

For the group of dubious cases the incidence of abnormal resting ECGs was somewhat lower, but the findings were in other respects consistent with those for the group with presumptive myocarditis.

The control group, on the other hand, showed significantly lower incidences of all abnormal findings with the exception of elevated antistreptolysin titers and sedimentation rates. Other abnormal findings were rare.

*Comparison of present and previous findings in cases of presumptive myocarditis.* The incidence of subjective symptoms at follow-up was found to be approximately 25 per cent, as compared to 75 per cent for the same series during convalescence 5 years earlier. In the earlier investigation 40 per cent of the patients with normalization of the resting ECGs had shown abnormalities on the exercise ECGs during convalescence. At follow-up, the exercise ECGs revealed abnormalities in 30 per cent of the patients, but almost 20 per cent had already shown abnormalities on the resting ECGs. The working capacity during convalescence had been abnormally low in some 60 per cent of a small series; the figure for this series 5 years later was approximately 40 per cent. Enlarged heart volumes had been recorded in 3 of 23 patients (13 per cent) as compared to 20 of 85 patients in the follow-up study.

**Discussion**

There are no established clinical criteria in the diagnosis of myocarditis. A tentative diagnosis of this condition is quite common, and for the analysis of a series of cases of myocarditis it is generally advisable to study a group of dubious cases along with a group in which the clinical diagnosis is reasonably certain. The present investigation demonstrates that two such groups may, even after 5 years, show a high degree of similarity.

The dubious group, however, had a significantly higher incidence of abnormal ECGs on orthostatic tests. Furthermore, the incidence of low working capacity and

enlarged heart volume was at least as high in this group as in the group of cases of presumptive myocarditis This finding may suggest that the dubious group included a number of patients with vasoregulatory asthenia—a state of deficient peripheral circulatory adjustment which besets the differential diagnosis between vasoregulatory asthenia and acute myocarditis [1 1 16 4 4] Differentiation is not possible except by direct determination of stroke volume during exercise as in heart catheterization

The third group which constituted the controls in this investigation had already been used for control purposes in studies of other series of patients in whom myocarditis was suspected [4] During the preceding 5 years however signs and symptoms not observed in the previous studies had emerged without any diagnosis of acute myocarditis and without any serious infectious disease of which the patients were aware This group nevertheless was found to include a few patients with abnormal exercise ECGs and low working capacities indeed at least one patient showed both electrocardiographic and other signs of acute myocardial lesions of the type here considered to be suggestive of acute myocarditis The abnormalities observed in the two groups probably represent in corresponding degree myocardial damage which had developed during the preceding 5 years The control series is too small however to permit any conclusion as to the incidence of myocarditis in an average population

As was to be expected the distribution shows that diseases of streptococcal etiology predominated constituting roughly one half of the total series —The incidence of acute myocardial lesions is known to be almost as high in cases of poliomyelitis [9 4] The series contains also a substantial number of cases of aseptic meningitis a circumstance which is consistent with several observations made in recent years [7] In point of fact both rheumatic fever and toxic scarlet fever have become more infrequent whereas aseptic meningitis has become increasingly common during recent years Among the various forms of aseptic meningitis Russian spring and summer encephalitis has received particular attention not least by virtue of its capacity to produce endarteritis in which respect the disease is of peculiar interest from the prognostic and functional standpoints [11]—The facilities available at that time did not permit examination of the present cases by virologic methods

In the main group of 90 cases abnormalities were most frequently observed in the exercise ECGs and less frequently in the resting ECGs alone or in both resting and exercise ECGs The investigation thus confirms as did the previous one [8] the value of exercise electrocardiography in myocarditis—a finding reported by several authors [12 13 ... 4 4 7 23 11 18] In the present series abnormal features were manifest in the resting ECGs alone in only 2 cases but in the exercise ECGs alone in 8 cases In the first two instances the abnormalities consisted of atrioventricular block in cases of rheumatic fever atrioventricular block is often difficult to evaluate on exercise electrocardiograms

In electrocardiographic studies of cases of myocarditis abnormalities of the terminal segment have invariably been the most common During convalescence however even disturbances in rhythm have not infrequently been recorded [1 ... 3 8] Although the same was true of the present investigation it applied remarkably enough chiefly to cases of nonstreptococcal infectious diseases In a few cases of poliomyelitis disturbances in rhythm were also noted on orthostatic tests The majority of abnormalities were found in the aseptic meningitis group which also had an incidence of reduced working capacity and enlarged heart volume at least as great as that in the rheumatic fever group These findings conflict with the earlier assumption that virus myocarditis invariably has a good prognosis *quoad restitutionem et quoad functionem* but they may be consonant with observations made by Weinstein in cases of poliomyelitis [43]

Under normal conditions there is a linear correlation between working capacity and stroke volume Similarly the stroke volume is linearly correlated with the heart volume [16] Under certain standardized conditions the intensity of exercise at a given heart rate is an indirect criterion of the stroke volume Hence the working

capacity may be correlated with the heart volume both at rest and during exercise (For further references see Sjöstrand[4, 41]) It may a priori be assumed that in the presence of myocardial lesions the working capacity will be reduced because of impaired myocardial contractility and a consequently reduced stroke volume More over in some cases circulatory insufficiency may result in an increase in the heart volume The corollary is that if in cases in which there is a certain degree of myocardial damage associated with reduced stroke volume and increased heart volume the working capacity is related either to an irrelevant factor such as the body weight or to a factor influenced by the disease such as the heart volume the latter correlation will be most likely to reveal a significant deviation from normal The foregoing conclusion is supported by the results of this investigation since correlation with the heart volume not only gave a distinctly higher incidence of abnormally low working capacity than did correlation with body weight but also showed in the individual cases more significant deviations from normal

Approximately one patient in five was found to have an enlarged heart volume and this incidence did not differ appreciably from group to group It should be emphasized that a heart volume determined in the erect position without accurate evaluation of the contours of the heart will not as a rule show abnormal enlargement in cases of myocarditis since the increased volume generally falls within the wide range of variation reported for current methods and the influence of orthostatic factors on the volume is not taken into account[9]

Comparison of the investigative results shows that enlarged heart volume and low working capacity were the two most frequently correlated findings followed by low working capacity and abnormal ECGs Although these three factors—abnormal ECG low working capacity and enlarged heart volume—were closely interrelated each of the first two factors was clearly correlated with the incidence of subjective symptoms and the first one was frequently concomitant with suspect phonocardiographic findings as well The most conspicuous correlation was that between enlarged heart volume and working capacity the weakest correlations were those between heart volume and respectively high antistreptolysin titers and suspect phonocardiographic findings (Table IX)

Subjective symptoms were correlated

*Table IX Incidence of abnormal and normal electrocardiograms working capacities and heart volumes in relation to subjective symptoms elevated antistreptolysin titers and/or sedimentation rates and suspect phonocardiograms*

| | Number of cases | Electrocardiogram | | | Working capacity | | | Heart volume | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Abnormal | Normal | Per cent abnormal | Abnormal | Normal | Per cent abnormal | Abnormal | Normal | Per cent abnormal |
| Subjective symptoms ‖ | 22 | 14 | 8 | 64 | 14 | 7 | 67 | 5 | 17 | 23 |
| Elevated antistreptolysin titer and/or E S R † | 25 | 15 | 10 | 43 | 14 | 11 | 56 | 5 | 20 | 20 |
| Suspect PCG findings‡ | 21 | 15 | 6 | 70 | 10 | 11 | 48 | 4 | 17 | 19 |
| Abnormal ECG§ | 41 | | | | 21 | 15 | 58 | 10 | 26 | 26 |
| Low working capacity | 34 | 20 | 14 | 59 | | | | 13 | 21 | 38 |
| Enlarged heart volume | 17 | 9 | 8 | 53 | 13 | 4 | 76 | | | |

[illegible]
†ASTT ≳ 400 u per milliliter E S R ≳ 20 mm per hour
‡[illegible] frequency and [illegible] diastolic [illegible]
§[illegible] cases the working capacity and heart [illegible]
‖Working capacity was not determined [illegible] case

with abnormal electrocardiographic findings and with low working capacity to about the same degree This observation is of practical clinical interest and corroborates the results of a previous investigation [1]

Recently Levander Lindgren examined 252 cases of myocarditis of different etiologies 6 months after the patients had been discharged from the hospital The results of the ECG examinations are rather similar to the results obtained in this series the frequency of persistent ECG changes at follow up was 20 per cent (mean) on examination at rest among various infectious diseases and rheumatic fever between 4 8 and 14 9 per cent and arrhythmia persisted in 45 per cent when the ECG at work was included However most of the patients were symptom free or had symptoms indicating neurocirculatory asthenia X ray of the heart and physical working capacity was mostly normal [a r]

In the present study comparison of the follow up results with those recorded by the same methods during hospitalization and convalescence of the patients 5 years earlier revealed a substantial decrease in the incidence of subjective symptoms The incidence of low working capacity had not declined to the same degree however and that of enlarged heart volume may well have risen although the latter comparison was not conclusive because of inequality in the number of cases compared In short the fact emerges that after presumptive myocarditis due to infectious disease the subjective symptoms gradually subside whereas electrocardiographic abnormalities reduced working capacity and enlarged heart volume may persist to a remarkably high degree

However we do not state that the clinical significance of our findings is of great importance The number of patients in our study was selected from an infectious diseases hospital material comprising approximately 15 000 patients and 5 years after discharge we found signs of persistent myocardial involvement in almost 30 to 40 cases yearly in only half of those might the involvement be suspected on routine examinations and rather few have any symptoms at all Most often the signs will appear as naevi pigmentosi (Levander Lindgren) of the electrocardiogram Nevertheless the sequelae of acute postinfectious myocarditis should not be overlooked for sometimes and we suppose more often than is suspected they are the adequate explanations for an arrhythmia a slight enlargement of the heart or an impaired physical condition The differential diagnosis particularly in instances of vasoregulatory asthenia vegetative disturbances neurosis and cardiosclerosis is often extremely difficult However in making the diagnosis the methods of exercise electrocardiography physical working capacity test and a sensible determination of heart size are very useful and are to be utilized

**Summary**

Ninety consecutive cases of acute infectious disease attended by signs highly suggestive of myocarditis ( presumptive myocarditis group ) were followed up after 5 years with examinations by the methods previously employed namely electrocardiography at rest during exercise and on orthostatic tests heart roentgenography and functional tests for determination of the physical working capacity Identical examinations were carried out in 26 similar cases in which 5 years previously there had been signs possibly suggestive of myocarditis ( dubious myocarditis group ) Finally the investigation included 34 cases of acute infectious disease in which at the onset 5 years earlier there had been no signs of cardiac involvement (controls)

Approximately 25 per cent of the 90 patients in the first group reported subjective symptoms—fatigue dyspnea impaired physical condition precordial pain—as compared to 75 per cent during prior convalescence The corresponding incidence in the control group was about per cent

At follow up about 25 per cent were found to have elevated antistreptolysin titers and or erythrocyte sedimentation rates the incidence being the same in the control group

Suspect phonocardiographic findings were recorded in 23 per cent (as against 3 per cent in the controls) but in no case were presystolic or diastolic murmurs noted

The resting ECGs were abnormal in 19 per cent, the exercise ECGs in 30 per cent, and the orthostatic ECGs in 10 per cent (0.6 and 12 per cent, respectively, for the controls). Sixty per cent of all abnormal ECGs were recorded either during or after exercise.

The majority of electrocardiographic abnormalities were referable to cases of aseptic meningitis, rheumatic fever, and scarlet fever. In most cases the abnormalities involved the terminal complex. In addition to these abnormalities some cases of rheumatic fever exhibited atrio-ventricular conduction block, and others disturbances in rhythm.

The working capacity was abnormally low in 41 per cent of all cases of presumptive myocarditis (and in 3 per cent of the controls), irrespective of the nature of the initial infectious disease.

The heart volume was enlarged in 20 per cent, possibly with a somewhat higher incidence for patients with aseptic meningitis and rheumatic fever than for those with other infectious diseases. No case of enlargement of the heart was found in the control group.

Abnormal findings were frequently interrelated, in particular, there was a high incidence of enlarged heart volume coincident with a low working capacity.

The incidences of abnormal findings were much the same in the "dubious myocarditis" group except for the orthostatic ECGs, which showed abnormalities in 27 per cent in comparison with about 10 per cent in the other two groups.

Abnormal findings were recorded in a few cases in the control series. Only in one or two patients were there signs that myocardial lesions had developed during the past 5 years.

To sum up, the over-all results of this 5-year follow-up study of 90 cases suggestive of postinfectious myocarditis (and compared with relevant control series) indicate that about 20 per cent of the patients still had subjective symptoms, some 15 to 20 per cent had abnormal ECGs, about 30 per cent had abnormal exercise ECGs, approximately 40 per cent had low working capacities and 15 to 20 per cent had enlarged heart volumes.

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# Effect of a new hypotensive drug, ST155, on the systemic circulation

Winifred G. Nayler, D.Sc.*
M. Rosenbaum, M.D., M.R.A.C.P.
J. McInnes, F.R.C.S., F.R.A.C.S.
T. E. Lowe, D.Sc., M.D., F.R.C.P., F.R.A.C.P.
Victoria, Australia

ST155 (2-(2,6-dichlorophenyl-1-amino)-imidazoline HCl) is a recently developed antihypertensive drug which, as is shown in Fig. 1, structurally resembles tolazoline. Although preliminary clinical trials indicate that it is an effective hypotensive agent, little is known about its mode of action. This paper describes a series of experiments planned to investigate the effect of ST155 on the systemic circulation of the dog.

## Materials and methods

Dogs on heart-lung bypass and dog isolated gracilis muscle preparations were used to investigate the effect of ST155 on the systemic circulation.

*Anesthesia.* Dogs were premedicated with 30 mg. of morphine sulfate intramuscularly approximately 1 hour before anesthesia was induced with sodium thiopentone (20 to 30 mg. per kilogram intravenously). A surgical level of anesthesia was maintained with a nitrous oxide-oxygen mixture (2:1) delivered from an intermittent positive pressure respirator at a rate of 2 liters per minute, with supplementary doses of thiopentone given from time to time as required.

*Dog heart-lung bypass preparation.* The method used has been described previously.[1] Anesthetized healthy mongrel dogs (12 to 15 kilograms) were heparinized (2 mg. per kilogram per hour intravenously) and placed on heart-lung bypass using a Kay-Cross disc oxygenator; the vascular system was perfused by means of a nonpulsatile (Mono) pump through the right common carotid artery at a constant flow rate which varied between 100 and 120 ml. per kilogram per minute in different experiments.

Appropriate cannulation allowed the independent measurement of venous outflow from the splanchnic, renal, lower inferior caval (IVC), superior vena caval (SVC), and azygos vascular fields and coronary sinus outflow. The mean systemic (arterial) pressure was indicated by a mercury manometer connected to a cannula inserted into either the left internal mammary or right femoral artery.

*Isolated gracilis muscle preparation.* This preparation has been fully described previously[2,3] and consists of an isolated gracilis muscle perfused under conditions of constant flow with heparinized (2 mg. per kilogram) blood warmed to 37° C. to

*From the Baker Medical Research Institute, Victoria, Aust.
This work was carried out during the tenure of a grant-in-aid from the National Heart Foundation of Australia.
Received for publication Feb. 4, 1966.
Address: Baker Medical Research Institute, Commercial Road, Prahran, S.1, Victoria, Australia.

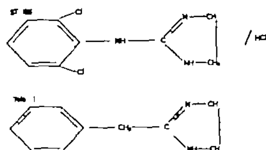



Fig 1 Structure of tolazoline and ST155

that changes in resistance to blood flow through the muscle are reflected as changes in perfusion pressure These changes were detected with a P23D(b) Statham strain gauge and displayed on an ultraviolet light photographic recorder *

*Drugs* The following drugs were used 2 (2 6 dichlorophenyl 1 amino) imidazoline HCl (as ST155†) sodium thiopentone (as Pentothal‡) epinephrine (as epinephrine tartrate§) norepinephrine (as Levophed bitartrate‖) pentolinium tartrate (as Ansolysen‡) phenoxybenzamine (as Dibenyline¶) propranolol (as Inderal#)

Dilutions of the various drugs were prepared in 0 9 per cent NaCl solution immediately before use Drug concentrations are expressed in terms of the salt

**Results**

*Effect of ST155 on the dog heart lung bypass preparation* In 12 experiments the administration of 5 μg/Kg of ST155 to the perfusion system of dogs on heart lung bypass was followed by an immediate transient rise and then a sustained fall in systemic perfusion pressure The results of a typical experiment shown in Fig 2 indicate that the phase of reduced perfusion pressure persisted for approximately 30 minutes after which it gradually returned to the initial level Doses of ST155 in excess of 5 μg/Kg caused a greater and more sustained decline in perfusion pressure The administration of a second dose of ST155 after all discernible effects of a first dose had disappeared was followed by a response which was identical with that recorded initially that is by an initial transient rise followed by a sustained fall in perfusion pressure

These biphasic changes in perfusion pressure were associated with a redistribution of blood throughout the various venous vascular fields During the initial transient phase of increased perfusion pressure SVC IVC and azygos blood flow decreased in all 12 experiments indicating probable vasoconstriction in these regional fields during this particular period of drug action Some of these changes are shown in Fig 3 Coronary blood flow increased during the phase of increased perfusion pressure as is shown in Fig 3 Splanchnic and renal flows remained relatively constant in all experiments

The initial pressor response caused by 5 μg/Kg of ST155 was not blocked by the prior administration of 15 mg/Kg of phenoxybenzamine a dose which is sufficient to abolish the pressor effect of 30 μg/Kg of epinephrine or norepinephrine

The phase of reduced perfusion pressure which followed the initial transient rise was associated with further changes in the regional distribution of blood In all 12 experiments blood flow through the IVC and azygos fields increased during the period of reduced perfusion pressure in 9 experiments the splanchnic blood flow increased Variable effects were found in the renal and SVC beds These results relating only to blood flow during the period of reduced perfusion pressure are summarized in Table I in which the arithmetic mean and the range of the ratios of blood flow and perfusion pressure before and after the administration of ST155 are listed In this table (Table I) the initial transient increase in perfusion pressure and the transient changes in regional blood flow associated with that initial increase have been omitted for the purposes of clarity During the phase of reduced perfusion pressure the coronary sinus blood flow showed a decline *relative* to that recorded during the period of increased perfusion pressure The data h

* Type 5124 C [illegible] Electrodynamics [illegible] C [illegible]
† [illegible] Pty Ltd A [illegible]
‡ May & Baker Ltd A [illegible]
§ David B [illegible] & C A [illegible]
‖ W [illegible] Laboratories A [illegible]
¶ Smith K[illegible] d F[illegible] A[illegible]
# Imperial Chem[illegible] Ind[illegible] E[illegible]

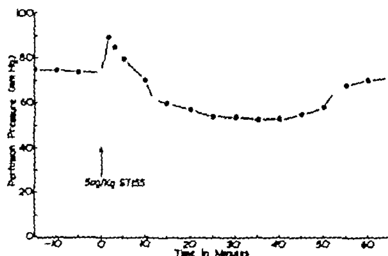



Fig. 2 Effect of ST155 on perfusion pressure in dog on heart lung bypass. Five micrograms per kilogram of ST155 was added at arrow as indicated. Preparation perfused under condition of constant flow throughout the experiment.

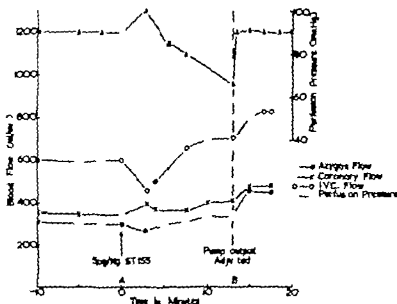



Fig. 3 Effect of ST155 on perfusion pressure and regional blood flow in dog on heart lung bypass. Under conditions of constant flow 5 µg/kg of ST155 was added at arrow *A* as indicated. At *B* after the hypotensive action of ST155 was established the volume output of the pump was readjusted to restore perfusion pressure to the original level and blood flow in the various vascular fields perfused at the control pressure and in the presence of ST155 was redetermined.

in Table II indicate however that in 11 of 12 experiments coronary sinus blood flow recorded during the period of ST155 reduced perfusion pressure was equal to or greater than that recorded during the initial control period before the administration of ST155.

*In 5 experiments approximately* 15 minutes after 5 µg/kg of ST155 had been administered to the preparation the volume output of the pump was adjusted to counterbalance the hypotensive action of ST155 and the perfusion pressure maintained at the initial control level. Under these conditions the action of ST155 was associated with marked increases in blood

*Table I Effect of 5 µg/Kg of ST155 on perfusion pressure and regional blood flow in dogs on heart lung bypass*

| Experiment No | Fractional change $\left(\frac{F}{I}\right)$ | | | | | | |
|---|---|---|---|---|---|---|---|
| | *Perfusion pressure* | *Coronary flow* | *IVC flow* | *Azygos flow* | *SVC flow* | *Splanchnic flow* | *Renal flow* |
| 12 | | | | | | | |
| Mean | 0 71 | 1 1 | 1 3 | 1 [illegible] | 1 0 | 0 97 | 0 88 |
| Range | 0 6–0 8 | 0 7–1 5 | 1 1–2 2 | 1 0–1 3 | 0 8–1 3 | 0 6–1 3 | 0 6–1 1 |

Mean [illegible] ratio $\frac{F}{I}$ [illegible] F = flow [illegible] perfusion pressure recorded during the hypotensive phase after the administration of 5 µg/kg of ST155 and I = control flow [illegible] perfusion pressure recorded immediately before the administration of ST155 Total body flow [illegible] constant throughout the experiment [illegible]

*Table II Effect of 5 µg/Kg of ST155 on perfusion pressure and coronary sinus blood flow in dogs on heart lung bypass*

| Experiment No | Perfusion pressure (mm Hg) | | Coronary sinus blood flow (ml /min ) | |
|---|---|---|---|---|
| | *Before ST155* | *After ST155* | *Before ST155* | *After ST155* |
| 1 | 85 | 65 | [illegible]85 | 287 |
| 2 | 75 | 55 | 470 | 441 |
| 3 | 90 | 60 | 165 | 206 |
| 4 | 120 | 80 | 149 | 193 |
| 5 | 95 | 80 | 236 | 285 |
| 6 | 95 | 70 | 196 | 170 |
| 7 | 90 | 70 | 236 | 363 |
| 8 | 95 | 70 | 272 | 280 |
| 9 | 100 | 80 | 175 | 200 |
| 10 | 90 | 60 | 171 | 194 |
| 11 | 90 | 65 | 337 | 390 |
| 12 | 90 | 60 | 187 | 19[illegible] |

[illegible] Coronary [illegible] blood flow [illegible] after the administration of ST155 [illegible] each experiment [illegible]

flow in the IVC SVC azygos and coronary vascular fields The results from a typical experiment are displayed in Fig 3 the other 4 experiments yielded similar results

In 5 experiments after the hypotensive action of ST155 had been established in a particular heart lung bypass preparation 10 mg /kg of pentolinium tartrate was administered followed 15 or 20 minutes later by the further administration of 5 µg/kg of ST155 The typical results of such an experiment are displayed in Fig 4 and indicate that the hypotensive action in dogs is blocked by the prior administration of pentolinium tartrate The initial pressor response however remained

In 6 other experiments the effect of 5 µg/kg of angiotensin on dogs on heart lung bypass was established before the administration of 5 µg/kg of ST155

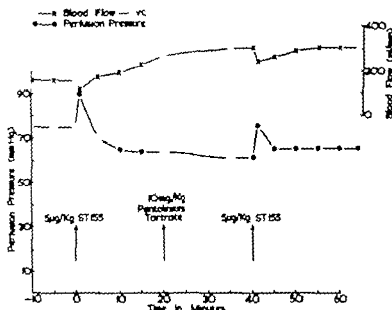



Fig 4 Effect of pentolinium tartrate on response of dog on heart lung bypass to ST155 Five micrograms per kilogram of ST155 was added at times as indicated before and after the addition of 10 mg /kg of pentolinium tartrate to dog on heart lung bypass perfused under conditions of constant flow

again during the hypotensive phase which followed the introduction of ST155 The results of these experiments are summarized in Table III and indicate that the effect of angiotensin on perfusion pressure and regional blood flow was only slightly diminished by the presence of ST155

ST155 was administered to 4 other preparations 15 minutes after the prior administration of 30 mg /kg of propranolol a dose which is sufficient to abolish the hypotensive effect of isoproterenol Under these conditions 5 to 10 μg kg of ST155 failed to produce any hypotensive effect the initial pressor response was still evident

*Effect of ST155 on the isolated gracilis muscle preparation* The addition of ST155 at 37°C to the perfusion system of isolated gracilis muscle preparations failed to cause a change in the perfusion pressure which was significantly greater than that caused by the control injection of saline The data listed in Table IV show that the addition of a wide range of doses of ST155 failed to exert any direct effect on the perfusion pressure in this isolated system

**Discussion**

These findings indicate that the administration of ST155 to dogs which are on heart lung bypass and in which the baroreceptor system has been left intact results in an immediate transient increase followed by a sustained fall in perfusion pressure These changes were found to be associated with changes in regional blood flow During the conditions of constant flow used in these experiments both perfusion pressure and total flow through individual vascular beds vary so that only over all trends in the resistance to blood flow through individual vascular fields can be ascertained

Immediately after the administration of ST155 the perfusion pressure increased reflecting an over all increase in total peripheral resistance which was not abolished by α adrenergic blockade During this transient phase of increased perfusion pressure skeletal muscle blood flow represented by the azygos lower IVC and part of the SVC flow decreased indicating vasoconstriction Some of these changes were shown by the data displayed in Fig 3 Coronary flow increased during this initial phase of increased perfusion pressure indicating either a lesser degree of vasoconstriction relative to that in other vascular fields or vasodilation

During the phase of reduced perfusion pressure muscle and coronary blood flow

*Table III Effect of 5 μg/Kg of angiotensin on systemic perfusion pressure and coronary and inferior vena caval blood flow in the presence and absence of 5 μg/Kg of ST155*

| Experiment No | Angiotensin (5 μg/Kg) | Before ST155 | | | After ST155 | | |
|---|---|---|---|---|---|---|---|
| | | Perfusion pressure (mm Hg) | Coronary flow (ml/min) | I.V.C. flow (ml/min) | Perfusion pressure (mm Hg) | Coronary flow (ml/min) | I.V.C. flow (ml/min) |
| 14 | Before | 110 | 492 | 413 | 95 | 555 | 577 |
| | After | 170 | 612 | 315 | 135 | 675 | 478 |
| 15 | Before | 75 | 353 | 355 | 45 | 331 | 572 |
| | After | 115 | 571 | 241 | 85 | 361 | 371 |
| 16 | Before | 100 | 231 | 315 | 75 | 319 | 413 |
| | After | 180 | 536 | 250 | 150 | 444 | 230 |
| 17 | Before | 95 | 239 | 462 | 60 | 353 | 557 |
| | After | 150 | 364 | 215 | 90 | 438 | 340 |
| 18 | Before | 85 | 182 | 462 | 7 | 222 | 600 |
| | After | 170 | 275 | 241 | 160 | 300 | 316 |
| 19 | Before | 110 | 214 | 231 | 80 | 300 | 275 |
| | After | 230 | 600 | 16[illegible] | 190 | 465 | 193 |

*Table IV Effect of ST155 on the perfusion pressure in the dog isolated gracilis muscle preparation*

| Experiment No | Perfusion pressure (mm Hg) | | | | | |
|---|---|---|---|---|---|---|
| | Control | After saline | After saline + ST155 (μg) | | | |
| | | | 1.0 | 0.1 | 0.001 | 0.0001 |
| 1 | 125 | 110 | 110 | 110 | | 110 |
| 2 | 100 | 95 | | 95 | 95 | |
| 3 | 110 | 100 | | 100 | | 100 |
| 4 | 95 | 90 | 90 | 90 | 90 | 90 |

increased indicating vasodilation Renal and splanchnic flows showed variable changes indicating either a lesser degree of vasodilation relative to that in the coronary and muscle beds or even vasoconstriction

In those experiments in which the volume output of the pump was increased in order to compensate for the ST155 induced fall in perfusion pressure muscle and coronary blood flow showed a marked increase when compared with that recorded at the same perfusion pressure prior to the addition of the drug Splanchnic and renal blood flows remained approximately at the control level indicating that ST155 had had little effect on the resistance to blood flow through these particular vascular fields

Although ST155 had a marked effect on skeletal muscle blood flow in the intact dog on heart lung bypass a direct act

on blood flow through the isolated gracilis muscle preparation was not detected These results may be interpreted to mean that ST155 acts centrally via the nervous system and this interpretation is supported by the complete blocking action of Ansolysen Since $\beta$ adrenergic blockade abolished the hypotensive action of ST155 it seems to be probable that the $\beta$ adrenergic receptors may be involved in the hypotensive action of this drug

**Summary**

Dogs on heart lung bypass and perfused gracilis muscle preparations were used to investigate the effect of the recently introduced hypotensive drug ST155 on the systemic circulation

Five micrograms per kilogram of ST155 caused a transient rise followed by a sustained fall in the perfusion pressure of dogs on heart lung bypass Changes in the regional distribution of blood were associated with these changes in perfusion pressure the hypotensive response being associated with a marked increase in muscle blood flow

Phenoxybenzamine failed to abolish the initial pressor action of ST155 propranolol and Ansolysen abolished its hypotensive action

ST155 failed to affect the perfusion pressure in isolated gracilis muscle preparations perfused under conditions of constant flow

We gratefully acknowledge the gift of ST155 from Boehringer Ingelheim Pty Ltd and of Inderal from Imperial Chemical Industries Phenoxybenzamine was kindly supplied by Smith Kline and French Pty Ltd

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# Changes in capillary filtration coefficient in the forearm during emotional and postexercise hyperemia and after intra-arterial adrenaline, acetylcholine, and isopropylnoradrenaline

*Jan Brod M D D Sc*
*Ivo Prerovsky M D C Sc*
*Milos Ulrych M D C Sc*
*Jiri Linhart M D C Sc*
*Horst Heine M D***
*Prague Czechoslovakia*

It has been repeatedly demonstrated that during the emotional reaction to stressful mental arithmetic blood flow increases markedly in the forearm and calf muscles[1-3] Barcroft[4] and Blair[5] and associates have produced evidence that this emotional vasodilation is at least partly mediated through sympathetic cholinergic fibers which are also thought to mediate the vasodilator response when a well defined hypothalamic area in cats is stimulated[6] The emotional vasodilation is only part of a generalized hemodynamic response consisting of vasoconstriction in the kidneys splanchnic area and skin and of an increase in cardiac output with a shift of blood to muscle[7] In this respect the reaction resembles the hemodynamic changes with muscular exercise Brod Hejl and Ulrych[8] have further demonstrated that whereas during muscular exercise blood flow increases in response to an increase in the metabolic demands of the muscle muscular hyperemia during emotion is not proportionate to any change in muscle metabolism and is independent of any change in the consumption of oxygen and glucose There is also some evidence based on the clearance rate of radioactive iodine ($I^{131}$) from muscle that the extra blood during emotional hyperemia in muscle flows through channels other than those used during a comparable increase in blood flow produced by muscular exercise

The question of a dual vascular pathway in muscle is open to discussion Its presence is claimed by some [1] but denied by most of the anatomists The method of KI 131 clearance is also open to criticism in view of a relatively slow diffusibility of this substance which may be a limiting factor during a marked increase in blood flow[11]

It would seem to be important therefore to investigate by other techniques the possibility of different blood channels during muscular exercise and emotion The size of the capillary surface area can be

F m k I [illegible] Cardiovascular Research Prague Czechoslovakia
Received for publication Feb 7 1966
Professor of Medicine Charles University Prague Director Institute for Cardiovascular Research [illegible] 809 [illegible]
Prague 4 Czechoslovakia
** Address: 2 d Department of Medicine, Charité Hospital, Berlin East Germany

assessed by the measurement of the capillary filtration coefficient (CFC)[15,16] provided that the permeability of the capillary wall does not change. This technique has also been used to investigate the influence of some of the substances thought to be important in mediating emotional hyperemia on capillary surface area.

**Methods**

The investigation was carried out on 23 volunteer subjects in a quiet laboratory in the morning hours after a light breakfast. Most of the subjects were suffering from various mild chronic conditions but had no evidence of impaired peripheral circulation in the upper extremities. The brachial artery and one of the veins in the left forearm were cannulated percutaneously by polyethylene catheters under local anesthesia, using Holmgren's modification[18] of the Seldinger technique.[17] Blood flow was measured by the mercury-in-rubber plethysmograph[18] placed in the middle of both forearms with the right forearm being used for control measurements.

The CFC was measured in both forearms using the increase in volume after an increase in pressure of 60 mm. Hg in the occluding cuff on the arm. After the rapid initial change, the increase in volume in the extremity between the third and fifth minutes after venous occlusion is approximately linear. This slope was used for measurement of the CFC. Venous pressure was registered simultaneously and was invariably stabilized at the time of measurement of the CFC. The effective capillary pressure available for filtration was assessed to be 80 per cent of the venous pressure, according to Mellander.[19] The CFC was expressed in milliliters per 100 ml. per minute per 1 mm. Hg.

Emotional stress was produced by having the subject subtract repeatedly a number from a preceding result at such a rate that he was unable to cope. The duration of this stimulus ranged from 10 to 15 minutes, during which time arterial pressure, blood flow, and CFC were registered. The procedure has been described previously.[7]

In the first 9 experiments in which the effect of muscular exercise was investigated, the subject lifted with his hand a weight of 3 kilograms at 2 second intervals for 2 to 3 minutes. In the other 6 investigations the subject was asked to open and close the fist rhythmically for 5 minutes at a rate that would produce a hyperemia comparable in degree to that produced by mental stress. Because of the technical difficulties in measuring the investigated parameters during actual exercise, the measurements were performed as soon as possible after cessation of the exercise, and assessments of blood flow were carried out before and after the estimation of CFC in order to ensure that the hyperemia persisted throughout the measurements. It is understood that this is not a steady state condition that is believed to be essential for the registration of the CFC. However, since accelerated blood flow was demonstrated both before and after the measurement of CFC, the registered CFC represents an integrated volume that was registered undoubtedly still before the postexercise hyperemia had subsided.

In another 13 subjects the influence of an infusion of acetylcholine, adrenaline, and isopropylnoradrenaline into the brachial artery of the experimental forearm was investigated. In order to exclude the possibility that the pharmacologic agents acted in some way other than only locally, the data were compared to those obtained simultaneously in the control forearms of all 10 subjects treated with isopropylnoradrenaline, in 5 of the 8 subjects treated with acetylcholine, and in 7 of the 8 subjects treated with adrenaline. The intra-arterial infusion was administered from a constant rate pump, and the dosage was adjusted in each individual subject so as to produce an increase in forearm blood flow comparable in degree to that produced by the period of stressful mental arithmetic. It ranged from 0.011 to 1.156 γ per minute for adrenaline, from 15.6 to 109.0 γ per minute for acetylcholine, and from 0.031 to 0.107 γ per minute for isopropylnoradrenaline. When several pharmacologic agents were tried in the same subject, a sufficient interval was allowed between infusions to ensure a return of forearm blood flow to a resting state. The patients did not complain of any undue discomfort.

The results were evaluated statistically using Student's t test.[20]

**Results**

*Muscular exercise and mental arithmetic.* In the first series of experiments, we compared CFC during postexercise muscle hyperemia with that accompanying stressful mental arithmetic in 9 subjects, and the data are summarized in the upper part of Table I. A typical result is demonstrated in Fig. 1. It may be seen that during postexercise hyperemia, CFC was markedly elevated from about 0.006 to 0.044 ml/100 ml/min/1 mm. Hg, but remained virtually unchanged or tended to decrease slightly during the hyperemia accompanying mental stress. Although muscle blood flow registered *immediately* on cessation of exercise was higher than flow during emotional stress, it decreased in the course of the postexercise period to levels comparable to those during mental arithmetic. However, the CFC during that period was still markedly elevated.

An analogous behavior of CFC during the postexercise hyperemia was noted in all of the 9 subjects. The increase in forearm blood flow in the postexercise period just before CFC was registered ranged from +33 to +221 per cent, with an average of +139 per cent ($p < 0.005$), whereas the increase in CFC ranged from +15 to +499 per cent, with an average of +177 per cent ($p < 0.025$). On the other hand, in the 8 experiments in which valid data on the CFC were obtained during emotional stress, forearm blood flow at the period closest to the measurement of the CFC was increased by +23 to +314 per cent, with an average of +140 per cent ($p < 0.005$), but the changes in the CFC were irregular and did not parallel changes in the forearm blood flow. They fluctuated between 50 and 161 per cent of the control value, the average change being 95.2 per cent for the whole group. Although the average values for the increase in forearm blood flow were practically of the same magnitude during emotion after exercise

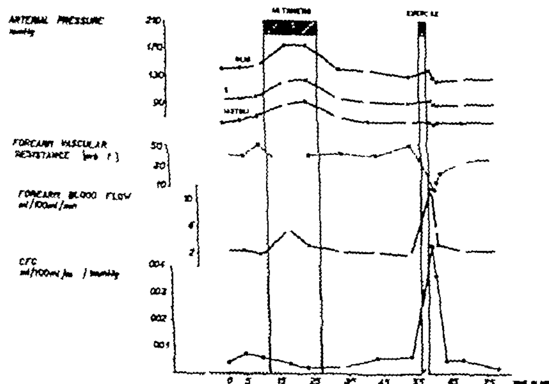



Fig. 1. Comparison of hemodynamic changes caused by emotional stress (mental arithmetic) and exercise ... Subject M.B.

*Table I Comparison of changes during stressful mental arithmetic and after exercise*

| Subject | Age | Sex | Diagnosis | | Arithmetic: Mean arterial pressure (mm Hg) | Arithmetic: Forearm blood flow (ml /100 ml /min ) | Arithmetic: Forearm vascular resistance (arbitrary units) | Arithmetic: CFC (ml /100 ml / min /1 mm Hg) | | Exercise: Mean arterial pressure (mm Hg) | Exercise: Forearm blood flow (ml /100 ml /min ) | Exercise: Forearm vascular resistance (arbitrary units) | Exercise: CFC (ml /100 ml / min /1 mm Hg) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 J K | 58 | M | Ischemic disease of lower extremities | b | 96 1 | 1 4 | 68 7 | 0 0044 | b | 107 0 | 1 5 | 71 4 | 0 0060 |
| | | | | A | 114 0 | 3 1 | 37 6 | 0 0030 | E | 95 0 | 4 8 | 19 8 | 0 0174 |
| | | | | % | 119 0 | 271 0 | 55 0 | 68 0 | % | 88 0 | 320 0 | 27 8 | 290 0 |
| 2 M V | 20 | M | Glomerular nephritis chronic | b | 122 0 | 2 1 | 57 3 | 0 0028 | b | 121 5 | 1 8 | 67 6 | 0 0033 |
| | | | | A | 130 0 | 4 8 | 27 1 | 0 0045 | E | 116 0 | 2 8 | 41 4 | 0 0045 |
| | | | | % | 107 0 | 2 8 0 | 47 0 | 161 0 | % | 96 0 | 155 0 | 61 3 | 136 0 |
| 3 J H | 51 | M | Ischemic disease of lower extremities | b | 95 7 | 1 3 | 76 0 | 0 0046 | b | 97 0 | 1 4 | 67 8 | 0 0024 |
| | | | | A | 108 0 | 5 2 | 21 0 | 0 0023 | E | 90 0 | 2 4 | 37 5 | 0 0068 |
| | | | | % | 113 0 | 400 0 | 28 0 | 50 0 | % | 92 8 | 171 0 | 55 4 | 284 0 |
| 4 M B | 19 | M | State after nephrectomy for congenital hydronephrosis | b | 97 0 | 2 3 | 42 2 | 0 0063 | b | 91 6 | 2 2 | 43 8 | 0 0064 |
| | | | | A | 122 4 | 5 7 | 21 5 | 0 0036 | E | 90 0 | 5 8 | 15 5 | 0 0371 |
| | | | | % | 128 0 | 248 0 | 51 0 | 57 0 | % | 96 0 | 262 0 | 35 0 | 599 0 |
| 5 K J | 62 | M | Varicose veins | b | 99 8 | 1 7 | 58 7 | 0 0037 | b | 105 0 | 1 8 | 60 0 | 0 0051 |
| | | | | A | 99 8 | 2 1 | 47 6 | 0 0025 | E | 104 0 | 6 3 | 16 5 | 0 0102 |
| | | | | % | 100 0 | 123 0 | 81 0 | 123 0 | % | 99 0 | 350 0 | 28 0 | 200 0 |
| 6 B J | 51 | F | Renal artery stenosis Hypertension | b | 94 8 | 1 5 | 63 2 | 0 0072 | b | 99 7 | 2 1 | 47 6 | 0 0070 |
| | | | | A | 119 5 | 2 3 | 52 0 | 0 0068 | E | 102 0 | 4 6 | 22 2 | 0 0201 |
| | | | | % | 126 0 | 153 0 | 82 0 | 94 0 | % | 103 0 | 218 0 | 46 0 | 287 0 |
| 7 F F | 57 | M | Essential hypertension | b | 102 0 | 2 2 | 47 4 | 0 0024 | b | 115 0 | 2 8 | 41 1 | 0 0039 |
| | | | | A | 116 0 | 9 1 | 12 8 | 0 0023 | E | 110 0 | 4 6 | 24 0 | 0 0045 |
| | | | | % | 104 0 | 414 0 | 27 0 | 96 0 | % | 96 0 | 164 0 | 59 0 | 115 0 |
| 8 J B | 30 | M | Mitral stenosis | b | 75 5 | 1 3 | 56 7 | 0 0046 | b | 81 0 | 1 5 | 54 0 | 0 0031 |
| | | | | A | 79 0 | 2 8 | 8 0 | 0 0052 | E | 76 0 | 2 0 | 38 0 | 0 0052 |
| | | | | % | 105 0 | 215 0 | 50 0 | 113 0 | % | 94 0 | 135 0 | 0 0 | 168 0 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 9 | V K | 50 M | Essential hypertension | b | 1 1 0 | 3 1 | 36 7 | 0 0039 | I | 129 0 | 2 6 | 50 6 | 0 0031 |
| | | | | A | 159 0 | 5 2 | 30 8 | — | I | 150 9 | 9 9 | 15 2 | 0 0100 |
| | | | | % | 1 5 0 | 158 0 | 84 0 | — | | 116 0 | 381 0 | 26 0 | 417 0 |
| | Mean (%) | | | | | 240 0 | 56 1 | 95 2 | | | 259 3 | 45 4 | 277 3 |
| | t | | | | | 4 073 | 6 013 | 0 365 | | | 4 514 | 9 784 | 3 474 |
| | p | | | | | <0 005 | <0 001 | n | | | <0 005 | <0 001 | <0 075 |
| 10 | Z L | 30 M | Chronic pyelonephritis | b | 101 5 | 3 1 | 33 8 | 0 0053 | b | 111 0 | 3 4 | 32 6 | 0 0078 |
| | | | | A | 115 0 | 6 6 | 18 5 | 0 0017 | I | 112 0 | 4 7 | 23 9 | 0 0031 |
| | | | | % | 113 0 | 211 0 | 55 0 | 89 0 | % | 101 0 | 138 0 | 73 0 | 120 0 |
| 11 | Z R | 28 M | Chronic glomerulonephritis | b | 119 0 | 1 8 | 31 1 | 0 0047 | b | 128 0 | 9 9 | 13 0 | 0 052 |
| | | | | A | 131 5 | 7 3 | 18 2 | 0 0015 | L | 123 0 | 23 4 | 5 3 | — |
| | | | | | 111 0 | 192 0 | 59 0 | 96 0 | % | 98 0 | 236 0 | 41 0 | — |
| 12 | V O | 49 M | Varicose veins | b | 107 2 | 3 0 | 33 7 | 0 0071 | b | 105 0 | 2 7 | 38 8 | — |
| | | | | A | 125 0 | 3 4 | 36 8 | 0 0092 | F | 108 0 | 18 6 | 5 8 | — |
| | | | | | 117 0 | 113 0 | 103 0 | 179 0 | % | 103 0 | 652 0 | 15 0 | — |
| 13 | V L | 28 M | Buerger's disease | b | 94 0 | 2 2 | 43 7 | 0 0081 | b | 96 0 | 3 7 | 25 9 | 0 0017 |
| | | | | A | 114 0 | 3 5 | 33 0 | 0 0024 | L | 95 0 | 6 0 | 13 8 | 0 0062 |
| | | | | | 126 0 | 159 0 | 76 0 | 29 0 | % | 99 0 | 162 0 | 61 0 | 132 0 |
| 14 | J V | 46 M | Nephrolithiasis | b | 97 3 | 3 4 | 28 6 | 0 0086 | b | 101 0 | 5 2 | 20 0 | 0 0066 |
| | | | | A | 145 0 | 11 1 | 13 1 | 0 0032 | L | 110 0 | 33 6 | 3 3 | 0 0100 |
| | | | | | 149 0 | 327 0 | 45 4 | 37 0 | % | 106 0 | 646 0 | 17 0 | 152 0 |
| 15 | F M | 44 F | Lymphedema | b | 107 0 | 3 1 | 32 9 | 0 0060 | b | 101 0 | 4 1 | 25 3 | 0 0068 |
| | | | | A | 1 7 0 | 9 5 | 13 3 | — | I | 112 0 | 13 4 | 9 8 | 0 0126 |
| | | | | | 125 0 | 310 0 | 40 0 | — | % | 109 0 | 278 0 | 38 8 | 184 0 |
| | Mean ( ) for 8 15 case | | | | | 231 6 | 58 9 | 87 7 | | | 286 4 | 38 7 | 97 2 |
| | t | | | | | 5 457 | 7 768 | 1 247 | | | 4 197 | 11 759 | 3 321 |
| | p | | | | | <0 001 | <0 001 | n | | | <0 005 | <0 001 | <0 005 |

A c elerall ase
CFC Capill ry filtrati ...

the fact demonstrated in Fig. 1 was obvious also in all of the other experiments namely that the first values after exercise were considerably higher than those observed throughout the entire period of the emotional stress. The similarity of the averages was due to the declining trend of the post-exercise blood flow during the period of observation.

In order to study the CFC at more comparable levels of blood flow at the beginning of the postexercise period and during mental arithmetic we carried out 6 additional experiments in which the exercise consisted of a mere opening and closing of the fist although this caused some difficulty because of the short duration of the postexercise hyperemia. These results are shown in the lower part of Table I. In 3 of the experiments however the volume curves were technically inadequate and in another subject (J V ) the increase in flow after exercise was again much higher than during emotion. In the other 2 subjects (Z L A L ) in whom the requirement of comparability of the increases in postexercise and emotional flows was fulfilled CFC was elevated after exercise and actually showed a drop during emotional stress.

The values of CFC recorded in subjects during comparable increases in flow after muscular exercise and mental stress are summarized in Fig. 2. They illustrate the fact that both stimuli increase forearm blood flow although the CFC rises only after muscular exercise and not during muscular hyperemia produced by mental stress. The difference in the reaction of the CFC during mental stress and after exercise at comparable flow levels is significant ($p < 0.025$).

*Pharmacologic agents.* The influence of adrenaline and acetylcholine was tested

*Table II. Changes during infusion of adrenaline*

| Subject | Age Sex | Diagnosis | | Mean arterial pressure (mm Hg) |
|---|---|---|---|---|
| 1 F R | 35 M | Essential hypertension | b<br>A | 12 0<br>12 0 |
| 2 J T | 42 M | Essential hypertension | b<br>A | 128 0<br>131 4 |
| 3 J I | 41 M | Varicose veins | b<br>A | 91 0<br>92 0 |
| 4 F C | 55 M | Essential hypertension | b<br>A | 145 0<br>143 0 |
| 5 J J | 38 M | Varicose veins | b<br>A | 96 0<br>89 0 |
| 6 M I | 26 F | Neurocirculatory asthenia | b<br>A | 121 0<br>120 0 |
| 7 S R | 41 M | Essential hypertension | b<br>A | 132 0<br>126 5 |
| 8 J V | 26 M | Chronic glomerular nephritis | b<br>A | 154 0<br>161 0 |

CFC Capillary filtration coefficient. E per. E perum mal. b Before. A Adrenaline.
The percentages were calculated from the protocol data and may differ insignificantly from those calculated from the rounded-out

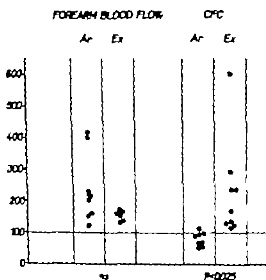



Fig 2 Changes in capillary filtration coefficient caused by emotion and exercise at a comparable increase in blood flow

in 8 subjects and the influence of isopropylnoradrenaline was studied in 10 subjects with overlapping. Isopropylnoradrenaline was included after we realized how difficult it is to maintain the hyperemia produced by the intra arterial infusion of adrenaline. The data are summarized in Tables II, III and IV.

The results were expressed as a per cent of the value expected if blood flow in the experimental forearm would change in a fashion parallel to that in the control forearm.

ADRENALINE. In 7 of 8 experiments adrenaline produced a rise in blood flow in the experimental forearm which ranged from 108 to 203 per cent of flow in the control forearm (Table II). The increased flow was due in all instances to a drop in the forearm vascular resistance. In 6 subjects the hyperemia persisted for more than 5 minutes. CFC fluctuated slightly on both sides of the resting values. In 7

| Forearm blood flow (ml./100 ml./min.) | | | Forearm vascular resistance (arbitrary units) | | | CFC (ml./100 ml./min./1 mm. Hg) | | |
|---|---|---|---|---|---|---|---|---|
| Exper | Control | % | Exper | Control | % | Exper forearm | Control forearm | % |
| 1 5 | — | — | 84 6 | — | — | — | — | — |
| 2 1 | — | | 60 7 | — | | — | — | |
| 3 4 | 3 2 | | 37 6 | 39 7 | | 0 0037 | 0 0011 | |
| 3 9 | 3 0 | 116 5 | 34 5 | 42 3 | 86 2 | 0 0048 | 0 0074 | 59 6 |
| 3 8 | 2 0 | | 23 7 | 45 6 | | 0 00 5 | 0 0081 | |
| 6 2 | 1 7 | 190 0 | 14 9 | 54 2 | 5 9 | 0 0061 | 0 009 | 40 3 |
| 6 9 | 4 0 | | 21 0 | 35 8 | | 0 0060 | 9 005 | |
| 13 0 | 5 7 | 203 0 | 11 2 | 38 1 | 50 5 | 0 0090 | 0 0067 | 118 8 |
| 4 7 | 4 | | 20 3 | 22 9 | | 0 0105 | 0 01 0 | |
| 4 2 | 3 4 | 109 5 | 21 2 | 26 2 | 90 1 | 0 0068 | 0 0142 | 8 1 |
| 1 3 | 1 | | 93 2 | 1 1 | | 0 0037 | 0 0039 | |
| 1 6 | 0 | 108 0 | 7 4 | 60 5 | 97 7 | 0 00 7 | 0 0047 | 60 6 |
| 9 | 1 9 | | 44 8 | 69 5 | | 0 009 | 0 0058 | |
| 4 1 | 1 4 | 188 5 | 30 8 | 90 3 | 51 8 | 0 011 | 0 0066 | 10 5 |
| 2 9 | 3 3 | | 54 0 | 49 4 | | 0 0061 | 0 005 | |
| 3 0 | 9 | 116 2 | 34 5 | 56 5 | 87 0 | 0 0045 | 0 0049 | 48 0 |

Appears ch tabl

*Table III Changes during infusion of acetylcholine*

| Subject | Age Sex | Diagnosis | | Mean arterial pressure (mm Hg) |
|---|---|---|---|---|
| 1 T R | 35 M | Essential hypertension | b<br>ACH | 127 0<br>128 0 |
| 2 J T | 42 M | Essential hypertension | b<br>ACH | 133 0<br>125 0 |
| 3 J L | 44 M | Varicose veins | b<br>ACH | 90 0<br>93 5 |
| 4 F C | 55 M | Essential hypertension | b<br>ACH | 144 0<br>141 5 |
| 5 J J | 38 M | Varicose veins | b<br>ACH | 90 0<br>86 5 |
| 6 M P | 26 F | Neurocirculatory asthenia | b<br>ACH | 118 5<br>112 5 |
| 7 S R | 41 M | Essential hypertension | b<br>ACH | 130 5<br>135 5 |
| 8 J V | 26 M | Chronic glomerular nephritis | b<br>ACH | 155 0<br>160 0 |

*CFC* Capillary filtration coefficient *Exper* Experimental *b* Before *ACH* Acetylcholine
The percentages were calculated from the protocol data and may differ insignificantly from the results calculated from the rounded-off

of these subjects comparison with the control forearm showed that a decreasing tendency was present in 5 whereas CFC remained virtually unchanged in the other 2 (102 3 and 113 8 per cent)

ACETYLCHOLINE Forearm blood flow was increased by acetylcholine in all 8 subjects and the forearm vascular resistance decreased in all of them (Table III) CFC increased by more than 0 0010 ml /100 ml /min /1 mm Hg in 1 subject (J T ) remained practically without change in 5 (T R J L F C M P J V) and decreased in 1 (J J) whereas the change could not be assessed with precision in the one other subject Comparable data with the other forearm were obtained in 4 subjects CFC showed an increasing trend (above 20 per cent) in 1 and did not exceed this arbitrary limit in the other 3 subjects

ISOPROPYLNORADRENALINE This drug produced a rise in the forearm blood flow of 107 5 to 397 0 per cent of the expected values in 9 of 10 subjects with a concomitant drop in the forearm flow resistance (Table IV) In the other subject (J V No 10) the resting blood flow recorded prior to infusion was still elevated after the preceding exercise despite a lapse of more than 30 minutes It is probably for this reason that no increase in flow could be demonstrated during the infusion of isopropylnoradrenaline CFC in this subject dropped to 78 9 per cent of the expected value In one subject the CFC increased by more than 20 per cent as compared with the other side (J V No 5) In 4 subjects the changes in CFC did not exceed the limit and in 3 the response of CFC was actually less on the experimental than on the control side (M P No 3 S R No 4 and Z L No 6) amounting only to from 30 7 to 67 3 per cent of the values on the control forearm In one sub

| *Forearm blood flow (ml /100 ml /min )* | | | *Forearm vascular resistance (arbitrary units)* | | | *CFC (ml /100 ml /min /1 mm Hg)* | | |
|---|---|---|---|---|---|---|---|---|
| *Exper* | *Control* | % | *Exper* | *Control* | % | *Exper forearm* | *Control forearm* | % |
| 1 9 | — | | 66 8 | — | | 0 0019 | — | — |
| 2 8 | — | | 45 7 | — | | 0 0019 | — | |
| 3 3 | — | | 40 3 | — | | 0 0078 | — | — |
| 9 2 | — | | 13 6 | — | | 0 0042 | — | |
| 4 0 | 1 7 | | 22 5 | 53 0 | | 0 0077 | 0 0091 | |
| 4 7 | 1 8 | 115 5 | 19 9 | 53 5 | 87 7 | 0 0086 | 0 0042 | 242 0 |
| 5 1 | 2 6 | | 25 0 | 55 4 | | 0 00 9 | 0 0069 | |
| 17 5 | 3 3 | 270 1 | 8 1 | 42 5 | 37 6 | 0 0072 | 0 0065 | 92 7 |
| 3 3 | 2 9 | | 27 3 | 31 1 | | 0 006 | 0 0129 | |
| 14 2 | — | | 6 1 | — | — | 0 0030 | — | — |
| 1 2 | 1 7 | | 103 1 | 72 3 | | 0 0078 | 0 0064 | |
| 2 1 | 1 6 | 187 0 | 53 6 | 70 5 | 57 6 | 0 0027 | 0 0056 | 108 2 |
| 2 8 | 1 7 | | 46 6 | 75 5 | | 0 0090 | 0 0058 | |
| 7 9 | 1 5 | 370 0 | 17 2 | 93 3 | 29 8 | — | — | — |
| 2 9 | 2 7 | | 53 5 | 57 5 | | 0 0037 | 0 0037 | |
| 12 9 | 2 5 | 490 0 | 12 4 | 64 0 | 20 4 | 0 0030 | 0 0030 | 100 0 |

Figure th c M

ject (A.L. No 9) the CFC could not be assessed with precision

**Discussion**

The method for measuring CFC is rather crude so that only large changes can be accepted as being meaningful It was important to keep this in mind in the experiments with mental stress which affects of course both extremities and where it was necessary therefore to use the same extremity as a control We have also proceeded in the same way in the analysis of the experiments with muscular exercise because these were done in the same subjects and during the same experimental session as the investigations with mental stress We thought that it would be more advantageous to analyze both sets of data in the same way the crucial point being the comparison of the behavior of the capillary bed during mental stress with that during muscular exercise

In the experiments with intra arterial infusion of the various pharmacologic agents we relied on the comparison of the changes in the experimental extremity with those in the control side in order to exclude a possible action of the drug which penetrated beyond the capillary bed of the experimental extremity and also to exclude spontaneous variations

The CFC can be considered to be an indicator of the number of patent capillaries[14] The increase in the number of capillaries that are open during muscular exercise has been well established since the time of Krogh[15] The marked and uniform increase in the CFC during the period after muscular exercise corroborates the validity of Folkow's assumption concerning interpretation of the CFC and is in keeping with changes in the CFC

*Table IX Changes during infusion of isopropylnoradrenaline*

| Subject | Age Sex | Diagnosis | | Mean arterial pressure (mm Hg) |
|---|---|---|---|---|
| 1 F C | 55 M | Essential hypertension | b | 140.5 |
| | | | I | 149.0 |
| 2 J J | 38 M | Varicose veins | b | 85.0 |
| | | | I | 76.0 |
| 3 M F | 26 F | Neurocirculatory asthenia | b | 117.5 |
| | | | I | 112.5 |
| 4 S R | 41 M | Essential hypertension | b | 132.0 |
| | | | I | 131.0 |
| 5 J V | 26 M | Chronic glomerular nephritis | b | 167.5 |
| | | | I | 155.0 |
| 6 Z I | 30 M | Chronic pyelonephritis | b | 111.0 |
| | | | I | 109.0 |
| 7 Z R | 28 M | Chronic glomerular nephritis | b | 124.0 |
| | | | I | 126.0 |
| 8 O V | 49 M | Varicose veins | b | 113.0 |
| | | | I | 117.6 |
| 9 A I | 28 M | Buerger's disease | b | 95.0 |
| | | | I | 97.0 |
| 10 J V | 46 M | Nephrolithiasis | b | 100.0 |
| | | | I | 103.5 |

*CFC* Capill[illegible] [illegible]
Th[illegible] [illegible]

reasons it is impossible to estimate capillary filtration during the actual exercise It is well known and has been also borne out by the data of our present work that immediately upon cessation of exercise muscle blood flow starts to drop In most experiments it follows an exponential like curve Although we have tried to start the measurements as soon as possible after exercise some time may be lost before the assessment of CFC can be begun It is very likely however that during the actual exercise the flow was even higher and the same might have been true of the capillary filtration rate Thus it may be objected that the measurement during the immediate postexercise period was not carried out under steady state conditions However our primary interest was not with the behavior of the muscle capillary bed during and after exercise this being well known—and our data are in keeping with the established facts The changes in the CFC during the postexercise muscular hyperemia were used simply for comparison with the behavior of the muscle capillaries during muscular hyperemia produced by emotional stress This did not change significantly the CFC although muscle blood flow exhibited an increasing trend in practically all experiments It may be argued that the difference between muscular exercise and mental arithmetic is due to the previously mentioned fact that at

| *Forearm blood flow* (ml /100 ml /min ) | | | *Forearm vascular resistance* (arbitrary units) | | | *CFC* (ml /100 ml /min /1 mm Hg) | | |
|---|---|---|---|---|---|---|---|---|
| *Exper* | *Control* | % | *Exper* | *Cont ol* | % | *Exper fo earm* | *Control forearm* | |
| 6 0 | 3 2 | | 23 4 | 43 2 | | 0 0064 | 0 0060 | |
| 9 4 | 2 8 | 181 5 | 15 8 | 53 2 | 54 9 | 0 0083 | 0 0072 | 106 5 |
| 2 7 | 2 4 | | 23 3 | 35 4 | | 0 0075 | 0 0070 | |
| 5 8 | 3 5 | 107 5 | 13 1 | 21 7 | 97 3 | 0 00 4 | 0 0059 | 118 9 |
| 1 5 | 2 6 | | 78 3 | 46 1 | | 0 0035 | 0 0051 | |
| 1 7 | 2 1 | 138 5 | 66 2 | 53 6 | 72 2 | 0 0037 | 0 0085 | 6 3 |
| 2 6 | 1 4 | | 30 8 | 94 3 | | 0 0100 | 0 0048 | |
| 4 1 | 1 7 | 191 5 | 32 0 | 109 0 | 52 2 | 0 0047 | 0 00 4 | 30 7 |
| 3 4 | 3 2 | | 49 7 | 52 5 | | 0 0058 | 0 0057 | |
| 4 2 | 3 5 | 112 9 | — | — | 87 0 | 0 0074 | 0 0013 | 138 0 |
| 3 1 | 5 1 | | 35 8 | 21 8 | | 0 0078 | 0 0043 | |
| 4 9 | 4 5 | 181 5 | 22 0 | 24 2 | 55 3 | 0 0012 | 0 0079 | 63 6 |
| 5 0 | 2 8 | | 24 8 | 44 3 | | 0 0037 | 0 0077 | |
| 5 6 | 2 2 | 207 0 | 7 8 | 53 0 | 18 9 | 0 0031 | 0 0067 | 115 5 |
| 2 8 | 2 4 | | 40 3 | 47 1 | | 0 0059 | 0 0066 | |
| 9 0 | 3 1 | 250 0 | 13 1 | 37 9 | 39 8 | 0 0043 | 0 0060 | 104 5 |
| 4 4 | 3 4 | | 21 6 | 27 9 | | | | |
| 6 9 | 4 2 | 128 0 | 16 7 | 26 5 | 78 8 | | | |
| 6 2 | 6 3 | | 14 4 | 15 4 | | 0 0081 | 0 0056 | |
| 3 9 | 6 1 | 65 0 | 26 1 | 16 8 | 153 3 | 0 0050 | 0 0043 | 8 9 |

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least immediately after muscular exercise muscle blood flow increased more than during emotional stress However if the opening of the capillary bed is dependent only on physical factors such as critical opening pressure[3] there should be no difference between the number of open capillaries if blood flow reaches the same level during postexercise hyperemia as during emotional hyperemia We have no reason to assume that the unchanged CFC during the emotional increase in blood flow would result from a decreased permeability of the capillary wall Hence the unchanged or even diminished CFC when forearm blood flow increases suggests that this extra blood during emotional hyperemia does not perfuse an increased filtering surface This is in agreement with our previous findings that show no change in the clearance rate of radioactive iodine ($I^{131}$) from muscle during the emotional increase in blood flow in the forearm Similarly there was no increase in the clearance rate of the intramuscularly injected xenon 133 during emotional hyperemia at least in part of the experiments carried out by Lassen (unpublished data) and ourselves (unpublished data)

It has been shown that emotional vasodilatation can be partly blocked by stellate ganglion anesthesia and atropine[4] This result suggested that vasodilatation is mediated by the cholinergic sympathetic

nervous fibers These are also involved in the muscular vasodilatation produced by stimulation of a well defined hypothalamic area[4,5] It was thought that the remainder of the vasodilatation after atropinization might be produced by circulating adrenaline which is corroborated by recent evidence of a diminished degree of emotional vasodilatation after β adrenergic receptor blockade by propranolol[6] Both acetylcholine and adrenaline are probably involved in the production of emotional vasodilatation If so an infusion of any of these substances in doses producing vasodilatation similar to that caused by the stress should also remain without effect on the CFC The results of our investigations are in full agreement with this assumption The difficulty of maintaining vasodilatation after adrenaline for a sufficient length of time necessary for the measurement of the CFC has been already mentioned since this substance acts on both alpha and beta receptors For that reason the effect of isopropylnoradrenaline (acting only on beta receptors) was also tested Although this substance produced vasodilatation in 9 of 10 observations CFC increased in 1 decreased in 3 and remained unchanged in 4 of the 8 subjects in whom valid data on CFC were obtained These data obtained with pharmacologic agents are in good accord with the findings of Kitchin[3] who has also studied the influence of intra arterial adrenaline on the CFC in the forearm of man The existence of a dual pathway of blood in forearm muscle is further corroborated by the studies with muscle clearance of KI 131 in cats[18] and in man[8]

Fencl and associates[19] have demonstrated that the emotional increase in forearm blood flow is located exclusively in muscle whereas the tone of cutaneous vessels increases during mental stress and skin blood flow remains unchanged during the rise in blood pressure It seems to be highly improbable also in view of the relatively low percentage of skin in the forearm that this would be connected with such a drop in cutaneous CFC to override the increase in muscle CFC after the use of pharmacologic agents In addition acetylcholine actually increases cutaneous blood flow The argument that our results were due to opposite changes of CFC in the muscle and skin which cancelled each other out seems therefore to be unlikely

Thus our data suggest that although in muscular exercise the extra blood entering the working muscle perfuses new capillaries the muscular hyperemia produced by emotion and also by the pharmacologic agents alleged to mediate this hyperemia is accomplished without such new capillaries being opened up Whether this extra blood passes through some as yet unidentified arteriovenous channels or whether it is simply accommodated by the pre existing capillaries through which blood flows at a higher speed is impossible to decide on the basis of the present experience

## Summary

1 Capillary filtration coefficient (CFC) in the forearm increases after exercise of the forearm muscle

2 An increase in blood flow during stressful mental arithmetic comparable in degree to the increase in blood flow after exercise either is not accompanied by any change in CFC or even leads to a drop in the CFC

3 Adrenaline acetylcholine and isopropylnoradrenaline which produce an increase in forearm blood flow do not effect any change in the CFC

We wish to thank Miss B Beckova and Miss E Kotanova for valuable technical assistance

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# Aortic flow and other hemodynamic responses to the Valsalva maneuver in the dog

*Howard Cohen, M.D.**
*Chicago, Ill.*

Since the work of Weber in 1851[1] the Valsalva maneuver (VM) has been recognized as a means by which the hemodynamic condition in man or the laboratory animal can be readily altered. The changes are quickly reversible with cessation of the VM.

Exhaling forcibly against the closed glottis produces hemodynamic changes by raising intrathoracic pressure and thus diminishes the intrathoracic blood content and impedes venous return to the right side of the heart. That blood is actually kept out of the thorax during the VM has been conclusively shown by means of $P^{32}$ and Diodrast injected into the deep abdominal veins.

The changes in blood pressure which occur when blood flow is temporarily impeded in this way have allowed the gleaning of much information concerning basic physiologic circulatory mechanisms and the effects of drugs and disease states on these mechanisms.[2-22]

Discussion in this presentation will be limited to the pressure overshoot (PO) of the VM. This pressure overshoot in the systemic arterial system occurs just after cessation of the VM. According to various investigators the PO is abolished by tetraethylammonium chloride,[4,5,7] norepinephrine,[4,6] previously existing high venous pressure,[6] bretylium tosylate, hexamethonium,[8] orthostatic hypotension,[11,12,13] significant heart failure,[16,17,19] significant mitral stenosis,[9,16,17] aortic stenosis,[16] constrictive pericarditis,[5,8] severe pulmonary vascular disease,[16,18,8,17] and occlusion of the common carotid artery.[14] Thus the VM has been used as a test to evaluate these drugs and disease states in the laboratory and even at the bedside.

Various mechanism have been postulated separately or in combination to account for the loss of the Phase IV response of the VM: (1) a venous pressure too high to be effectively impeded by the VM so that no pool of blood will have stagnated and be ready to go through to the left side when the VM is released;[6] (2) a weakened myocardium which will not respond with forceful contractions to the onrush of the released blood;[16,19] (3) a blunting of the normal reflex peripheral vasoconstriction so that even when the blood pool is passed rapidly through the left side of the heart peripheral resistance is too low to elicit a rise above control blood pressure;[4,18,21] (4) a mechanical obstruction such as a stenotic valvular lesion or severe pulmonary vascular disease preventing the pooled blood from advancing through the left side with enough velocity to effect an overshoot;[16,18] (5) maximal vasoconstric-

From the Cardiovascular Institute and the Division of Cardiovascular Disease, Department of Medicine, Michael Reese Hospital and Medical Center, Chicago, Ill.
Supported in part by Grant HE 8252 from the National Heart Institute, United States Public Health Service.
Received for publication Feb. 10, 196[illegible].
*Address: Michael Reese Hospital and Medical Center, 29th St. and Ellis Ave., Chicago, Ill. 60616.

tion at the onset of the VM as with nor epinephrine allowing no further vasocon striction after release of the VM and thus no overshoot[25]

No one has demonstrated with certainty the actual mechanism of the *normal* over shoot One reason for this is that there has not been until recently a good method of measuring instantaneous aortic flow in the intact animal Without such measure ments of flow it cannot be determined whether the rise in pressure during the pressure overshoot is due to an increase in blood flow or an increase in peripheral resistance (vasoconstriction) or to a com bination of the two Although ganglionic blocking agents abolish the PO thus in the absence of concomitant measurements of flow does not prove that the normal over shoot *must* be based on va oconstriction It only means that the normal overshoot might not be seen when *marked* vasodilata tion pre exists Flows have been measured with indicator dilution methods[3] and have suggested that flow is actually decreased during the pressure overshoot implying that the PO is due solely to peripheral vasoconstriction This method however does not give instantaneous flows and flow values averaged over a period of time cannot be compared with instantaneous pressures in these circumstances Thus changes in resistance or peripheral vaso constriction cannot be determined at any given moment in time Such information can be obtained at least in the laboratory animal by using the electromagnetic flow meter

The purpose of this study was to deter mine the simultaneous conditions of blood pressure blood flow and peripheral re sistance in the systemic arterial system during the PO (Phase IV) of the VM in anesthetized dogs It will be shown that almost always a flow overshoot accom panies the pressure overshoot and that peripheral resistance may be increased or decreased during the PO of the VM

**Methods and materials**

One hundred sixteen VMs were induced in 13 mongrel dogs (male and female) weighing from 12 to 18 kilograms anesthe tized with sodium pentobarbital in a dose of 25 mg per kilogram An endotracheal rubber cannula with a balloon cuff was secured in place and an ordinary blood pressure cuff was placed around the thorax An aneroid sphygmomanometer was con nected by plastic tubing into a single pres sure system with the compressed air source the 2 liter glass reservoir and the endo tracheal tube and blood pressure cuff The reservoir could be filled and then suddenly opened into the entire system so that the resultant pressure was 25 mm Hg Intra pulmonary pressure therefore also reached 25 mm Hg The pressure could be released simply by disengaging the tubing from the endotracheal cannula (see Fig 1) This system for simulating the VM is similar to one previously described[24]

Arterial pressures obtained through poly ethylene catheters inserted via the femoral or carotid artery were recorded on a San born multichannel direct writer Aortic flows were obtained by placing a Medicon Model M4001 electromagnetic flowmeter probe on the arch of the aorta through an incision in the lower left thorax and the flow was recorded on the Sanborn writer (Fig 2) Positive pressure artificial respira tion was used during surgery With the flowmeter probe in place the chest was closed airtight the pneumothorax was re duced through a 20 gauge needle and the animal was allowed to resume spontaneous respiration Pressure during the VM was

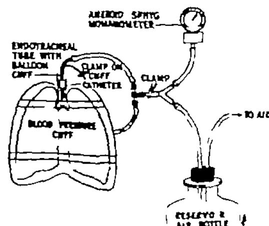



Fig 1 Diagrammatic representat of the method of induci g the Valsal a maneu er the closed chest dog The reservoir r bottle w nected to a compressed tap

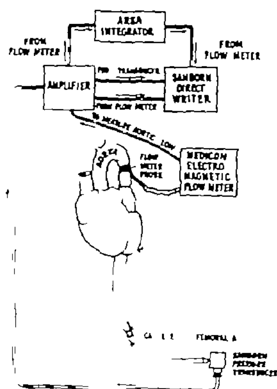



Fig. 2. Diagram ... representation of the method of measuring ... arterial pressure and aortic flow.

maintained until arterial pressure began to rise (second part of Phase II of the VM).

## Results

Fig. 3 shows a typical trial with the Valsalva maneuver.

Of the 116 trials in which systemic arterial flows and pressures were obtained there were 80 in which the typical pressure overshoot was present and 36 in which it was absent. A flow overshoot was detected in 80 trials and was absent in 36 (Tables I and II). (Flow refers to flow per beat.*)

Of the 80 trials with a pressure overshoot there were 72, or 90 per cent, which had concomitant flow overshoots. Thus in only 10 per cent was the typical pressure overshoots of the VM not associated with an increase in flow.

Of 68 trials with a concomitant peak instantaneous flow rate overshoot (as distinguished from flow per beat), 30, or 44 per cent, had a greater increase in flow than in pressure when expressed as per cent of their respective control values (see

*Flow per beat was used to indicate ch... in fl... during the overshoot. Peak instantaneous flow rate (flow rate) was compared with the correspond... pressure t... d term... the periph... ral resistance ... point in time.

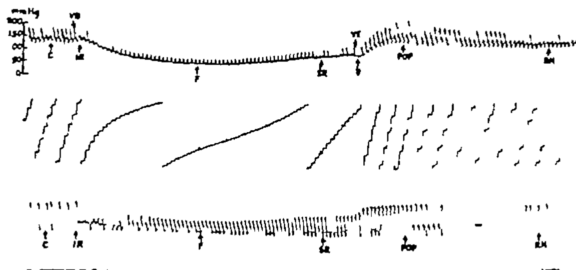



Fig. 3. Typical response to Valsalva maneuver. *Top curve*: Systemic arterial pressure. *Bottom curve*: Aortic flow rate. 10 mm = 3,750 c.c. per minute. *Middle curve*: Aortic flow from area of flow rate curve. 5.5 mm = 12 c.c. of flow. *C*: Control. *IR*: Initial rise. *F*: Fall during sustained compression. *SR*: Secondary rise. *D*: Drop with release of Valsalva. *POP*: Pressure overshoot period. *RN*: Return to normal. *FOP*: Flow overshoot period. *VB*: Valsalva begins. *VE*: Valsalva end. Intrapulmonary pressure was 25 mm. Hg. Time (*bottom line*) in seconds.

*Table I. Summary of trials showing pressure overshoot*

| Induced Valsalva maneuver in the dog<br>80 Trials showing pressure overshoot in Phase IV | |
|---|---|
| Trials with concomitant flow overshoot—72 (90%) | Trials without concomitant flow overshoot—8 (10%) |

Note: Percentages refer to ratio of stated number of trials to number of trials in immediately preceding box. All flows refer to flow per beat.

*Table II. Summary of trials without pressure overshoot*

| Induced Valsalva maneuver in the dog<br>36 Trials showing no pressure overshoot in Phase IV | |
|---|---|
| Trials with flow overshoot—18 (50%) | Trials without flow overshoot—18 (50%) |

Note: Percentages refer to ratio of stated number of trials to number of trials in immediately preceding box. All flows refer to flow per beat.

*Table III. Summary of trials showing pressure overshoot*

| Induced Valsalva maneuver in the dog<br>80 Trials showing pressure overshoot in Phase IV | | | |
|---|---|---|---|
| Trials with concomitant flow rate overshoot—68 (85%) | | Trials without concomitant flow rate overshoot—12 (15%) | |
| *Trials* | *Peripheral resistance* | *Trials* | *Peripheral resistance* |
| 30 (44%) | Fall | 12 (100%) | Rise |
| 34 (50%) | Rise | | |
| 4 (6%) | No change | | |

Note: Percentages refer to ratio of stated number of trials to number of trials in immediately preceding box. All flows refer to peak instantaneous flow rate.

*Table IV. Summary of trials without pressure overshoot*

| Induced Valsalva maneuver in the dog<br>36 Trials showing no pressure overshoot in Phase IV | | | |
|---|---|---|---|
| Trials with flow rate overshoot—17 (47%) | | Trials without flow rate overshoot—19 (53%) | |
| *Trials* | *Peripheral resistance* | *Trials* | *Peripheral resistance* |
| 17 (100%) | Fall | 16 (84%) | Fall |
| | | 1 (5%) | Rise |
| | | 2 (11%) | No change |

Note: Percentages refer to ratio of stated number of trials to number of trials in immediately preceding box. All flows refer to peak instantaneous flow rate.

Tables III and IV). This indicates that in these cases there was a *decrease* in peripheral resistance, a vasodilatation. In 34 (50 per cent of those with both flow rate and pressure overshoots) the pressure increased percentagewise more than the flow rate. Thus these pressure overshoots were due to an increase in both flow rate and peripheral vasoconstriction. In 4 trials (6 per cent of those with both a pressure and flow rate overshoot) the flow rate and pressure overshoots were equal and denoted no change in peripheral vasoconstriction.*

Of the 36 trials with no pressure overshoot, 47 per cent showed a flow rate overshoot indicating a peripheral vasodilatation. In the remaining 19 trials both pressure and flow rate fell but to different degrees: 16 showed a decreased and 1 showed an increased peripheral resistance, and 2 showed no change.

Thus in 116 trials peripheral resistance decreased in 63, or approximately 54 per cent; increased in 47, or 41 per cent; and remained the same in 6, or about 5 per cent.

## Discussion

Classically, the changes in arterial pressure associated with the Valsalva maneuver are divided into four phases. Phase I is a

*With the [illegible] of peripheral resistance [illegible] (1). [illegible] were [illegible] the [illegible] thoracic aorta, [illegible] whereas flow was measured at the beginning of the descending aorta. Because of this, and because of the differences in response time of the measuring devices, the curves of flow rate and pressure were not synchronous. Correction for this was attempted by using the peaks of each of the curves. These peaks varied no more than 0.05 second. ( ) It is recognized that peripheral dilatation during Phase IV may be due to active vasodilatation, loss of active vasoconstriction, or passive vascular dilatation because of changes in blood volume associated with the flow overshoot in this phase of the Valsalva maneuver.

short initial rise in pressure immediately after straining has begun Phase II is the subsequent marked drop in pressure followed by a slow rise Phase III is the sudden short drop in pressure when the straining is released Phase IV is the overshoot which is followed by a return to normal Phase I is associated with a bradycardia initiated by the initial rise in pressure Early in Phase II the bradycardia may become more marked possibly because of vagal stimulation by the expanded lungs Later during Phase II there is a tachycardia initiated by low blood pressure and hypoxia With Phase IV a bradycardia occurs which is associated with an overshoot in pressure and a decrease in hypoxia These changes in heart rate indicate the presence of intact sympathetic and parasympathetic pathways

In the present study almost every pressure overshoot was associated with a bradycardia and was preceded by a tachycardia indicating that these autonomic pathways were intact

In those trials in which no pressure overshoot was seen 47 per cent had a flow rate overshoot signifying that the pressure overshoot had been lost solely because of peripheral vasodilatation probably secondary to the anesthesia In the other 53 per cent there was no flow rate overshoot Surgical trauma to the heart great vessels and lungs may have prevented the rapid inflow of blood in Phase IV and explain the loss of the flow and pressure overshoots

The main points brought out in this study concern the 80 trials which demonstrated *the classic pressure overshoot* In 90 per cent a flow overshoot was present. This is in agreement with the classic concepts of these events but contrary to evidence cited when indicator-dilution curves were used

Forty four per cent of the trials showing a concomitant flow rate overshoot showed a decrease in peripheral resistance The data presented here have demonstrated that in the dog under the conditions of these experiments a flow rate overshoot alone can effect the typical pressure overshoot of the Valsalva maneuver This is also suggested by recent work in human beings[20]

**Summary**

1 One hundred sixteen Valsalva maneuvers were performed on 13 anesthetized closed chested dogs and recordings were made of aortic flow with an electromagnetic flowmeter and of aortic pressure with catheters threaded into the femoral or carotid arteries

2 Of 36 trials which showed no pressure overshoot during Phase IV half showed a flow overshoot In 47 per cent loss of pressure overshoot was ascribed to peripheral vasodilatation The other 53 per cent showed that a drop in flow rate (or flow rate and peripheral resistance) was the etiology of the loss of pressure overshoot

3 In 80 trials demonstrating a pressure overshoot during Phase IV of the Valsalva maneuver 72 (90 per cent) showed a concomitant flow overshoot Of the 80 pressure overshoots 30 showed a decrease in peripheral resistance during the overshoot

4 This study supports the classic concept that there is a flow overshoot associated with the pressure overshoot of the Valsalva maneuver It also indicates that the pressure overshoot can occur in the face of decreased peripheral resistance in dogs under the conditions of this experiment

I should like to acknowledge the assistance of Dr L J Hirsch Dr A B Shaffer and Dr L N Katz in the planning of these experiments and in the preparing of the manuscript I am indebted to Messrs A Ellis A Rose and N Jones for their technical assistance.

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# Beta-adrenergic blockade in experimental myocardial infarction

*Brian L. Pentecost, M.D., M.R.C.P.**
*W. Gerald Austen, M.D.***
*Boston, Mass.*

Beta adrenergic blockade by the agent pronethalol or its analogue propranolol has been evaluated clinically in the treatment of angina pectoris[1-4] and recently its use has been suggested in the management of acute myocardial infarction.[5] Inhibition of the positive chronotropic and inotropic effects of sympathetic stimulation on the heart could beneficially result in reduced oxygen requirement of the myocardium after myocardial infarction; also the antiarrhythmic properties of pronethalol and propranolol[6-8] could prevent those serious arrhythmias which frequently claim the lives of patients with relatively small areas of myocardial damage. However, beta receptor antagonists reduce myocardial contractility[9-11] and may, in addition, inhibit the coronary vasodilator response to anoxia.[12,13] These effects would be potentially hazardous in the presence of myocardial injury and anoxia after infarction.

The following study was designed to investigate the effect of partial beta adrenergic blockade on the survival rate of dogs submitted to coronary artery ligation. Propranolol was utilized at two dose levels and observations were made to determine the presence of myocardial depression.

## Materials and methods

Twenty adult mongrel dogs weighing 10 to 18 kilograms were used. After anesthesia had been induced with intravenous thiopental, a cuffed endotracheal tube was inserted and ventilation was maintained by a positive pressure respirator delivering a 50 per cent mixture of oxygen in air. Thoracotomy was performed through a median sternotomy and the pericardium was excised from the anterior aspect of the heart. The heart was rotated to the right for sufficient time to allow dissection of the circumflex artery, around which was placed an untied ligature 5 to 8 mm. from its origin. Then the heart was replaced in its normal position in the posterior portion of the pericardial sac. The external iliac artery and vein were cannulated in order to measure central arterial and venous pressures through strain gauge transducers; the pressures were recorded continuously on a Sanborn direct writing multichannel recorder. Cardiac output was measured by the Cardio Green method using a Gilford arterial cuvette and a Harvard constant withdrawal pump. The electrocardiogram (ECG), Standard Lead II, was recorded from subcutaneous electrodes.

At the outset of each experiment three

From the Department of Surgery, Harvard Medical School, and the General Surgical Services, Massachusetts General Hospital, Boston, Mass.
Received for publication on Feb. 21, 1967.
Supported in part by United States Public Health Service Grants [illegible] HF-080 1 and HE-06664(HLPI).
*Physician, Queen Elizabeth Hospital, Birmingham, England; Visiting Research Fellow, Massachusetts General Hospital.
**Associate Professor of Surgery, Harvard Medical School; Associate Visiting Surgeon, Massachusetts General Hospital.

estimations of cardiac output were made over the course of 20 minutes together with pressure and electrocardiographic records at paper speeds of 25 and 100 mm per second before either administration of drugs or coronary ligation. The animals were then treated in one of three ways. In the first group of 7 dogs no propranolol was administered before coronary ligation and these served as a control series. In the second group of 6 dogs propranolol was infused intravenously over 3 minutes to a total dose of 0.2 mg per kilogram and after a 10 minute period further measurements of cardiac output and pressure were made before the circumflex artery was ligated. In the third group of 7 dogs propranolol was infused in a similar manner to a dose level of 0.08 mg per kilogram; further measurements of output and pressure were made as in the second group and the circumflex coronary artery was ligated. In all dogs after coronary artery ligation the ECG and arterial and venous pressures were monitored continuously and estimations of cardiac output were made at 1, 5, 30, 45 and finally at 60 minutes after ligation, at which latter time the experiment was terminated. In each experiment effective coronary artery ligation was confirmed at the end of the study. When the dog failed to survive after coronary artery occlusion the time and mode of death were noted. Left ventricular work, tension time index and systolic ejection rate were calculated from the available data using Formulas 1-3.* The systolic ejection period in systolic seconds per minute was obtained from the central aortic pressure by measuring the time from the beginning of the upstroke to the incisura and multiplying by the heart rate.

In all calculations of standard deviation the sample number = n-1. The cardiovascular results of infusing propranolol were statistically evaluated by means of a two sample ranking test; comparisons of the hemodynamic results of coronary occlusion in the three groups were treated similarly. The significance of survival rates in the three groups after myocardial infarction was assessed by calculating chi squared.

## Results

Hemodynamic data recorded at the beginning of each experiment are summarized in Table I. There was no significant difference between the three groups of dogs initially.

*Cardiovascular effects of intravenous propranolol.* The results of infusion of propranolol were qualitatively similar at the two dose levels (Table II). The heart rate and cardiac output were reduced in all dogs. Only with the high dose infusion was there a significant increase in mean arterial pressure. Left ventricular work was reduced in all but one dog after infusion of propranolol; there was also a significant fall in the tension time index. Although the duration of each systole was increased as a result of beta adrenergic blockade, there was no over all change in systolic ejection rate because of the accompanying bradycardia and fall in cardiac output.

*Effects of circumflex coronary artery occlusion.* All animals showed electrocardiographic evidence (in Lead II) of myocardial infarction with elevation of S-T and subsequent T wave inversion. Table III shows a significantly increased survival rate among the dogs pretreated with 0.08 mg of propranolol when compared with the control series ($p < 0.05$). Although the survival rate was greater in the dogs treated with the high dose of propranolol than in the control group, the difference did not reach statistical significance at the 5 per cent level.

The hemodynamic changes brought about by circumflex artery ligation recorded 1 to 2 minutes after occlusion are

(1) Left ventricular work (kg M./min.) = C[illegible] output (L./min.) × 13.6 × M[illegible] ... (mm. Hg) / 1,000

(2) Tension time index (mm. Hg sec./min.) = M[illegible] arterial pressure (mm. Hg) × S[illegible] systolic ejection period (sec./min.)

(3) Systolic ejection rate (ml./systolic sec.) = C[illegible] output (ml./min.) / Systolic ejection period (sec./min.)

*Table I. Initial hemodynamic data*

| Group | Number of dogs | Cardiac output (ml./min.) | | Mean arterial pressure (mm. Hg) | | Heart rate (beats/min.) | |
|---|---|---|---|---|---|---|---|
| | | Average | ± S.D. | Average | ± S.D. | Average | ± S.D. |
| Controls | 7 | 888 | 400 | 96 | 19 | 156 | 24 |
| Propranolol (0.2 mg./Kg.) | 6 | 905 | 253 | 91 | 14 | 175 | 11 |
| Propranolol (0.08 mg./Kg.) | 7 | 896 | 290 | 93 | 19 | 145 | 24 |

*Table II. Hemodynamic responses to intravenous propranolol at two dose levels*

| | Before infusion | After propranolol (0.2 mg./Kg.) | Per cent change | | Before infusion | After propranolol (0.08 mg./Kg.) | Per cent change | |
|---|---|---|---|---|---|---|---|---|
| | | | Average | ± S.D. | | | Average | ± S.D. |
| Cardiac output (ml./min.) | 905 | 789 | −13 | 13.0 | 896 | 717 | −20 | 9.5 |
| | | | $p < 0.05$ | | | | $p < 0.01$ | |
| Stroke volume (ml.) | 5.25 | 6.50 | +24 | 12.7 | 6.3 | 6.6 | +4.5 | 14.4 |
| | | | $p < 0.05$ | | | | $p > 0.10$ | |
| Mean arterial pressure (mm. Hg) | 91 | 98.5 | +7 | 9.5 | 93 | 93 | 0 | 7.5 |
| | | | $p < 0.05$ | | | | $p > 0.10$ | |
| Heart rate (beats/min.) | 175 | 12 | −30.5 | 7.4 | 145 | 109 | −25 | 5.8 |
| | | | $p < 0.01$ | | | | $p < 0.01$ | |
| Left ventricular work (Kg. M./min.) | 1.12 | 1.04 | −7.5 | 7.1 | 1.11 | .94 | −15 | 7.4 |
| | | | $p < 0.05$ | | | | $p < 0.01$ | |
| Tension time index (mm. Hg sec./min.) | 1,940 | 1,672 | −14 | 11.1 | 1,949 | 1,659 | −15 | 10.8 |
| | | | $p < 0.05$ | | | | $p < 0.05$ | |
| Systolic ejection rate (ml./systolic sec.) | 44.7 | 46.0 | +3 | 8.00 | 41.1 | 40.2 | −2 | −8 |
| | | | $p > 0.10$ | | | | $p > 0.10$ | |

*Table III. Mortality within 60 minutes of coronary artery ligation*

| Group | Number of dogs | Deaths | Time of death (range) |
|---|---|---|---|
| Control | 7 | 6 | 1 min. 50 sec.—4 min. 40 sec. |
| Propranolol (0.2 mg./Kg.) | 6 | 3 | 4 min.—5 min. 40 sec. |
| Propranolol (0.08 mg./Kg.) | 7 | 1 | 3 min. 45 sec. |

detailed in Table IV. Animals receiving the higher dose of propranolol showed a significantly greater depression of cardiac output and mean arterial pressure than did the control dogs ($p < 0.05$). The calculated systolic ejection rate and left ventricular work were also more depressed in the animals treated with propranolol ($p < 0.01$). Dogs in the third group (propranolol 0.08 mg. per kilogram) generally tended to show hemodynamic results midway between those of the other two groups, but these were not significantly different from those encountered in either Group 1 or 2. The reduction in the tension time index was similar in all three groups of dogs.

Of the 4 propranolol treated dogs which

*Table IV. Comparison of hemodynamic status of dogs before and 1 to 2 minutes after coronary artery occlusion*

| | Initial values | Postocclusion values | Per cent change: Average | Per cent change: ± S.D. |
|---|---|---|---|---|
| Control dogs | | | | |
| Mean pressure (mm. Hg) | 97 | 73 | −25 | 15.3 |
| Cardiac output (ml./min.) | 888 | 707 | −19.5 | 13.5 |
| Systolic ejection rate (ml./systolic sec.) | 44.3 | 39.6 | −10 | 14.0 |
| Left ventricular work (Kg.M./min.) | 1.0/7 | 0.704 | −33 | 17.4 |
| Tension time index (mm. Hg sec./min.) | 1,960 | 1,313 | −33 | 1 0 |
| Propranolol (0.2 mg./Kg.) | | | | |
| Mean pressure (mm. Hg) | 91 | 36 | −39 | 13.3 |
| Cardiac output (ml./min.) | 905 | 4 6 | −48 | 20.0 |
| Systolic ejection rate (ml./systolic sec.) | 46.8 | ?7.5 | −41 | 22.7 |
| Left ventricular work (Kg.M./min.) | 1.170 | 0.369 | −67 | 16.5 |
| Tension time index (mm. Hg sec./min.) | 1,946 | 1,6/2 | −24 | 18.7 |
| Propranolol (0.08 mg./Kg.) | | | | |
| Mean pressure (mm. Hg) | 93 | 1 | −73 | 33.6 |
| Cardiac output (ml./min.) | 896 | 593 | −34 | 15.0 |
| Systolic ejection rate (ml./systolic sec.) | 44.1 | 3? 3 | −? | 17.0 |
| Left ventricular work (Kg.M./min.) | 1.110 | 0.5 8 | −47.5 | 2 6 |
| Tension time index (mm. Hg sec./sec.) | 1,950 | 1,314 | −2 3 | 21.6 |

died. 3 had severe depression of cardiac output and mean arterial pressure 1 to 2 minutes after coronary occlusion. Among the majority of survivors arterial pressure improved after the initial depression. At 60 minutes after coronary occlusion mean arterial pressure among the 9 propranolol-treated survivors was 93 per cent of the initial value, whereas cardiac output was little changed at 63 per cent of the control level (Fig. 1).

All nonsurvivors developed ventricular fibrillation within 6 minutes of coronary occlusion, frequently preceded by ventricular tachycardia. Ventricular ectopic beats were seen frequently in survivors treated with propranolol. 1 dog developed 4:1 atrioventricular heart block, and 2 showed evidence of transient intraventricular block.

**Discussion**

There was a significant improvement in the survival rate among dogs receiving 0.08 mg. per kilogram of propranolol. One possible explanation of this finding may be that beta-adrenergic blockade modifies the function of the heart in a manner that reduces the oxygen requirements of the myocardium. In this way myocardial hypoxia around the margins of the infarcted area would be minimized and the consequent ventricular irritability avoided.

Consumption of oxygen by the myocardium has been demonstrated to be determined by the tension developed in the myocardium as expressed by the tension time index,[14] although it is probably the initial process of generation of pressure[15] and the velocity of contraction[15] rather than its duration which is the critical factor in determining the oxygen needs of the myocardium. Thoracotomy in the dog results in diminished heart size, lowered cardiac output and mean arterial pressure, and a tachycardia.[7] Propranolol, by slowing the heart rate and leaving the arterial pressure only slightly elevated or unchanged, reduced the tension time index of the preparation in spite of a prolongation of each individual systole, and therefore probably reduced the oxygen requirement of the myocardium just before coronary artery ligation. Left ventricular work was reduced to a greater extent

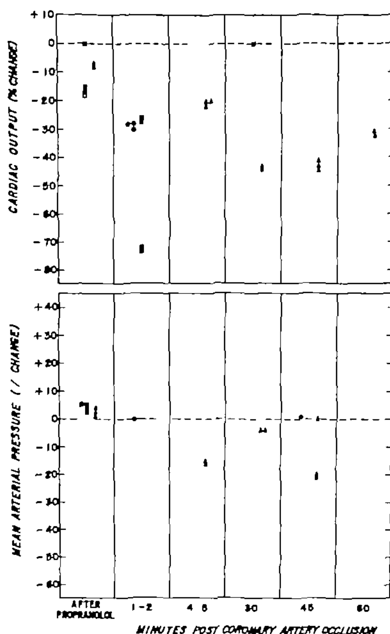



Fig. 1. Changes in cardiac output and mean arterial pressure after infusion of propranolol and circumflex coronary artery occlusion. *Open circles*: Control nonsurvivors. *Open squares*: Propranolol 0.2 mg./Kg., nonsurvivors. *Open triangles*: Propranolol 0.08 mg./Kg., nonsurvivors. *Solid circles*: Control survivors. *Solid squares*: Propranolol 0.2 mg./Kg., survivors. *Solid triangles*: Propranolol 0.08 mg./Kg., survivors.

than was the tension time index because of the reduction in cardiac output, but volume work appears to be of less importance than pressure work in determining myocardial oxygen consumption and coronary blood flow.[11,13] After coronary artery ligation, there was, however, a similar reduction in the tension time index in all three groups. Thus, there is some evidence that propranolol reduced the oxygen needs of the myocardium before coronary ligation, but no evidence of a different hemodynamic response to infarction between the control and low dose propranolol groups. Although the two dose levels of propranolol produced similar results before coronary occlusion, the survival rate was significantly improved only in the dogs receiving 0.08

mg per kilogram of propranolol. This finding may depend upon depression of myocardial contractility as a result of greater loss of sympathetic stimulation at the higher dose. Sympathetic stimulation is known to increase myocardial contractility,[11,12] and 3 of the 4 nonsurvivors receiving propranolol showed a profound reduction in cardiac output and mean arterial pressure after coronary ligation. In addition, the systolic ejection rate was depressed to a greater degree after coronary ligation in the high dose group than in the other experimental groups.

The high incidence of ventricular fibrillation after coronary artery ligation in this experiment may be related to the tachycardia in the open chest dog which increases myocardial oxygen requirements, and the beneficial effects of propranolol may be more difficult to demonstrate in the intact animal. The ability of pronethalol and propranolol to slow the heart rate at rest and during exercise has been shown in man,[8,17] and a tachycardia after myocardial infarction may be an oxygen wasting situation correctable by these agents. However, in this study, the risks of myocardial depression have been shown to be real in 2 animals at the high dose level and in 1 at the low dose level of propranolol. It has been demonstrated that a slow infusion of beta adrenergic blocking agents results in lesser degrees of myocardial depression[5] than does a rapid injection, but the appropriate dose for each individual patient might be difficult to determine.

Alternatively, the improved survival rate after propranolol may depend on the antiarrhythmic properties of these drugs. Propranolol has been shown to protect against arrhythmias induced by adrenaline[4] and ouabain[25] in the dog, and this property may be independent of its beta adrenergic blocking action.

**Summary**

Experimental myocardial infarction was produced in dogs by ligation of the circumflex coronary artery. Six of 7 control animals died in ventricular fibrillation within 6 minutes of coronary ligation. Only 1 of 7 dogs which were pretreated with propranolol (0.05 mg. per kilogram) died after the same procedure, whereas the mortality rate was not significantly altered by pretreatment with propranolol at a higher dose (0.2 mg. per kilogram). There was evidence of greater depression of cardiac function after coronary artery ligation in the dogs receiving the higher dose of propranolol. The mechanism of the protective action of propranolol against ventricular fibrillation in the ischemic myocardium is discussed and its attendant dangers are indicated.

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# The prevention by glucocorticoids of endotoxin initiated thrombosis in rat, in relation to fibrinolysis, coagulation, and lipemia

*Serge Renaud, M.D., Ph.D.*
*Claude Allard, Ph.D.*
*Jean G. Latour, M.Sc.***
*Montreal, Canada*

Contradictory results have been reported concerning the effect of corticoids on blood coagulation[1] and on atherosclerotic and thrombotic phenomena. In Cushing's syndrome characterized by various hormonal imbalances, the unusually severe atherosclerotic lesions have been generally attributed to adrenal hyperactivity. However, long-term administration of glucocorticoids in man does not appear to cause an increase in aortic sclerosis but rather a regression of the intimal lesions. In the rabbit it seems to be well established[4-7] that the administration of glucocorticoids inhibits the cholesterol-induced atherosclerosis, although it can increase the cholesterolemia. With regard to thrombosis, it has been reported that long-term treatment with ACTH or cortisone in man can be followed by thromboembolic complications,[8] although other authors[9] concluded that the administration of cortisone is rarely followed by thromboembolisms and that cortisone can be given safely to patients with coexisting heart disease. In the hamster it seems that cortisone treatment predisposes to platelet thrombosis.[10]

In recent years[11-14] we have been able to initiate, by the injection of gram-negative bacteria endotoxins in hyperlipemic rats, a thrombotic phenomenon particularly suitable for experimental studies. Since, as briefly mentioned above, there is no agreement in the literature concerning the effect of cortical hormones on coagulation and conditions generally associated with atherosclerosis, this problem was investigated in the rat in the experiments reported in the present communication. Our studies included the effects of several corticoids on the blood coagulation, the fibrinolytic activity, and some lipemic parameters of hyperlipemic rats in which phlebothrombosis was induced by an endotoxin injection.

## Materials and methods

In these experiments 254 Holtzman male rats with an initial body weight of 140 to 150 grams were utilized. The animals were housed 6 per cage in a constant

From the Laboratories [illegible] of Experimental Pathology [illegible] Medical Research [illegible] Montreal, Canada.

This work was supported by Grant MA-1444 from the Medical Research Council and by [illegible] from the Quebec Heart Fund.

Received for publication Feb. 28, 1966.

*Sponsored by the [illegible] Laboratory of Experimental Pathology [illegible] Montreal, Que., Canada.

**Fellow of the National Research [illegible]

temperature environment and given ad libitum tap water and the following hyperlipemic diet described in detail elsewhere[14] butter 38 casein 11 cellulose* 15 cholesterol 5 salt mixture† 4 sodium cholate 2 sucrose 23 and vitamin mixture‡ 2 (weight per cent) The animals were fed the diet for 9 weeks (Series I Gr 5 to 8) or 11 weeks (Series I Gr 1 to 4 and Series II and III)

The corticoids were administered in the form of an aqueous suspension at the dose and for the duration indicated in the appropriate table Heparin was injected subcutaneously after being diluted as follows Depo-heparin § 200 mg gelatin 2 Gm dextrose 1 Gm and distilled water quantity sufficient to 24 ml

At the end of the feeding periods and after 17 hours of fasting a volume of blood corresponding to approximately 1 per cent of the body weight was removed in siliconized syringes from the jugular veins of all of the rats under ether anesthesia This blood was utilized for determination of the fibrinolytic activity (Series II and III) of the plasma clotting time (Series III) or of the lipemic parameters (Series III)

The fibrinolytic activity was determined in diluted blood according to the technique of Billimoria and collaborators[14] with the following modifications before sterilization the glassware and needles were siliconized according to the technique reported by Bauer[19] Blood 0 9 ml was drawn into a 2 ml syringe containing 0 1 ml of sodium citrate (3 8 per cent) mixed and then transferred to a tube maintained in crushed ice and containing 17 ml of the phosphate buffer (pH 7 4) In each of 4 screw capped tubes 1 ml of the diluted blood was added to 1 25 units of thrombin in 0 05 ml of physiologic saline The tubes were inverted twice to ensure mixing kept for 30 minutes at 4 C incubated at 37°C and then placed in crushed ice two of the tubes having been incubated for 1 hour and the other two for 3 hours The clots were filtered as described previously[14] on glass cloth washed with 10 ml of cold saline and then placed in tubes in 10 ml of 0 1 N NaOH The tubes were then incubated for 5 minutes at 100°C and read at 290 mμ in a Beckman spectrophotometer (Model DU) to measure the tyrosine content of the clot Preliminary experiments under the conditions used here showed that the peak absorption for tyrosine was 290 mμ and that the optical density was inversely proportional to the incubation time particularly between 1 and 3 hours The fibrinolytic activity as measured by the difference in the optical density between 1 and 3 hours of incubation was expressed in per cent clot lysis and is reported in the tables as such

The plasma recalcification time in siliconized tubes was determined as follows all the glassware was siliconized After a few drops of blood had been drawn for other purposes the syringe was removed and with the same needle 0 9 ml of blood was collected in a syringe containing 0 1 ml of sodium citrate (3 8 per cent) After thorough mixing with the citrate in the syringe the blood was transferred to a centrifuge tube kept at 30 C After 6 minutes of centrifugation at 2 000 r p m the plasma was removed and also kept at 30°C until the test was performed Experiments to be published elsewhere showed that at this temperature the plasma clotting time remains practically constant for several hours Next 0 1 ml of the plasma was added to 0 1 ml of sterile physiologic saline and incubated for 10 minutes at 37°C before the addition of 0 1 ml of 0 025 M $CaCl_2$ After 1 minute the tube was tilted gently every 10 seconds until a firm clot formed The test was performed in duplicate The determinations of cholesterol triglycerides and lipoprotein in serum were made according to the techniques utilized in previous studies[14]

Immediately after withdrawal of blood for laboratory tests the rats were given by the same needle 1 ml per 100 Gm body weight of physiologic saline containing a *Salmonella typhosa** lipopolysaccharide (0 6 mg per kilogram) The survivors were killed 24 hours after in

*Alphacel Nutritional Biochemicals Co
†Salt mixture Wesson Nutritional Biochemicals Co
‡Vitamin diet fortification mixture Nutritional Biochemicals Co
§Upjohn Company

*0901 Boivin type Difco Laboratories

jection of the endotoxin autopsy was performed on every animal and the incidence of red hepatic infarcts was recorded

The macroscopic readings were verified by histologic examination of the left hepatic lobe As already reported [22, 23] the incidence of hepatic infarcts corresponds exactly to the incidence of occlusive thrombosis

**Results**

*Series I* (*Table I*) When injected with the *S typhosa* lipopolysaccharide animals fed the hyperlipemic diet for 11 weeks but otherwise untreated (Gr 1) presented a 100 per cent incidence of multiple red hepatic infarcts resulting from obstruction of the hepatic veins by thrombi and described *in detail elsewhere* [22, 23] *In addition* there was a 16 per cent incidence of anemic renal infarcts due to thrombosis of the interlobar or arcuate arteries and an 88 per cent mortality rate None of the animals fed the diet for 11 weeks and injected with hydrocortisone (Gr 2) prednisolone (Gr 3) or ACTH (Gr 4) died in the 24 hours after injection of the endotoxin and the incidence of thrombosis varied from 0 to 33 per cent in these groups The cardiac infarcts which were at the apex or involved a large part of the left ventricle were due to obstruction of a coronary artery by a thrombus usually at a bifurcation (Figs 1 2 and 3) In the animals fed the hyperlipemic diet for 9 weeks but otherwise untreated (Gr 5) injection of the endotoxin induced thrombosis only in the hepatic veins the incidence being 83 per cent The mortality rate in this group was only 25 per cent In the remaining groups fed the diet for 9 weeks those treated with hydrocortisone (Gr 6) presented an incidence of thrombosis of only 33 per cent those with fluorohydrocortisone (Gr 8) an incidence of 50 per cent and those with desoxycorticosterone (Gr 7) an incidence of 83 per cent In addition although in Groups 6 and 8 no mortality was recorded Group 7 presented a mortality rate of 66 per cent

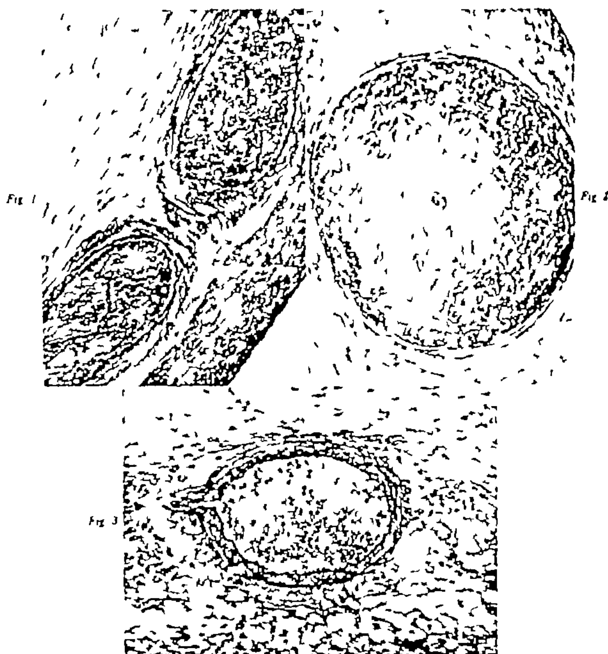
*Series II* (*Table II*) In this series all *the groups were fed the hyperlipemic diet* for 11 weeks In the first part of the series a single injection of distilled water (Gr 1) or prednisolone (Gr 2) was administered to the animals 2 hours before the determination of blood fibrinolytic activity and the injection of endotoxin The fibrinolytic activity was significantly lower in Group 2 than in Group 1 Although the incidence of infarcts was the same in both groups the mortality rate was 83 per cent in Group 1 but there was no mortality in the group injected with prednisolone

In the second part of this series (Gr 3 4 5) distilled water (Gr 3) or prednisolone

*Table* I *Effect of ACTH and some steroid hormones on the production of endotoxin initiated thrombosis*

| *Group* | *Number of rats* | *Feeding period (wk)* | *Hormone* | *Infarct incidence (%)* | | | *Survival (min)* | *Mortality (%)* |
|---|---|---|---|---|---|---|---|---|
| | | | | *Hepatic* | *Renal* | *Cardiac* | | |
| 1 | 18 | 11 | None | 100 | 16 | 0 | 540 ± 96 | 88 |
| 2 | 6 | 11 | Hydrocortisone (3 mg) | 16 | 16 | 16 | 1440 ± 0 | 0 |
| 3 | 6 | 11 | Prednisolone (1 mg) | 0 | 33 | 16 | 1440 ± 0 | 0 |
| 4 | 6 | 11 | ACTH (4 I U) | 16 | 16 | 16 | 1440 ± 0 | 0 |
| 5 | 12 | 9 | None | 83 | 0 | 0 | 1190 ± 153 | 25 |
| 6 | 6 | 9 | Hydrocortisone (3 mg) | 33 | 0 | 0 | 1440 ± 0 | 0 |
| 7 | 6 | 9 | Desoxycorticosterone (3 mg) | 83 | 0 | 0 | 702 ± 210 | 66 |
| 8 | 6 | 9 | Fluorohydrocortisone (0 2 mg) | 50 | 0 | 0 | 1440 ± 0 | 0 |

Mean ± S E
The hormones were injected subcutaneously [illegible] 72 48 24 and 1 hour [illegible] the ACTH [illegible] 72 48 40 24 16 [illegible] before the injection of endotoxin
The animals were [illegible] of the *S typhosa* [illegible] lipopolysaccharide [illegible] hyperlipemic diet for 9 [illegible] 11 weeks




Figs *1-3* Histologic appearance at different levels of a thrombus in the left coronary artery of a hyperlipemic rat injected with an endotoxin (periodic acid Schiff ×140). *Fig 1* The head of the thrombus at a bifurcation. *Fig 2* The medial part of the thrombus. Note the huge dilatation of the vessel occluded by the thrombus and the resulting stretching of the wall as compared to the same vessel in Fig 3. *Fig 3* The normal size coronary artery containing the tail of the thrombus invaded by polymorphonuclear leukocytes.

(Gr 4 and 5) was injected once a day for 4 days, the fibrinolytic activity being determined and the endotoxin administered 2 hours after the last injection. The fibrinolytic activity was still significantly lower in Group 4 than in Group 3. However, the incidence of hepatic infarcts was only 28 per cent in Group 4 as compared with 93 per cent in Group 3. In Group 5, in which in addition to the injections of prednisolone, EACA (Epsilon amino caproic acid) was administered by stomach tube 2.5

*Table II Influence of prednisolone on blood fibrinolytic activity and the production of endotoxin initiated thrombosis in hyperlipemic rats*

| Group | Number of rats | Treatment | % Clot lysis | | Infarct incidence (%) | | | Mortality (%) |
|---|---|---|---|---|---|---|---|---|
| | | | Mean ± S E | p Values | Hepatic | Renal | Cardiac | |
| 1 | 6 | Distilled water (1 day) | 47 ± 6 | | 83 | 16 | 16 | 83 |
| 2 | 6 | Prednisolone (1 day) | 24 ± 5 | <0 02 | 83 | 16 | 0 | 0 |
| 3 | 14 | Distilled water (4 days) | 42 ± 7 | | 93 | 14 | 14 | 85 |
| 4 | 14 | Prednisolone (4 days) | 19 ± 5 | <0 02 | 28 | 14 | 14 | 21 |
| 5 | 11 | Prednisolone + EACA (4 days) | 1 ± 0 8 | <0 01 | 2[illegible] | 18 | 0 | 0 |

Prednisolone (1 mg) [illegible] 0.5 ml of distilled water [illegible] the same volume of distilled water [illegible] was injected subcutaneously [illegible] once daily
EACA (Epsilon [illegible]) 1.5 Gm/kg was given by stomach tube 2.5 hours before the injection of endotoxin
The [illegible] by the [illegible] of *S typhi* lipopolysaccharide 2 hours after the last dose of hormone [illegible] fed the hyperlipemic diet for 11 weeks

hours before the endotoxin the fibrinolytic activity was only 1 per cent The incidence of infarcts in this group however was no different from that in Group 4 treated with prednisolone only although no mortality was recorded

*Series III* (*Table III*) All the rats were fed the hyperlipemic diet for 11 weeks In the first part of the series distilled water (Gr 1) or hydrocortisone (Gr 2) was injected once only 2 hours before the removal of blood for the various determinations and the administration of endotoxin There was no significant difference between Groups 1 and 2 in the parameters determined except for the percentage of clot lysis which was significantly reduced in Group 2 In this latter group however the mortality rate was only 23 per cent as compared with 64 per cent in Group 1

In the second part of the series distilled water (Gr 3) or the hormones (hydrocortisone Gr 4 and 5 desoxycorticosterone Gr 6) were injected for 7 days the last injection being given 2 hours before the removal of blood and the administration of endotoxin Group 4 presented a lower fibrinolytic activity than Group 3 but a much longer clotting time and a much higher percentage of α lipoproteins (p < 0 001) In this former group the peak of the α lipoproteins did in fact migrate ahead of the albumin zone and these lipoproteins were identified as α + pre-α The peak of the α 2 lipoproteins in addition to being markedly depressed was also ahead of the α 2 globulins and consisted of α 1 + α 2 lipoproteins The triglyceride level however was significantly higher in Group 4 than in Group 3 (p < 0 05) The incidence of hepatic infarcts was reduced from 85 (Gr 3) to 14 per cent (Gr 4) and the mortality rate from 54 to 4 per cent by the hydrocortisone treatment Administration of EACA in addition to hydrocortisone (Gr 5) completely inhibited the fibrinolytic activity However the plasma clotting time and the incidence of infarcts in Group 5 were comparable to those in Group 4 In Group 6 the administration of desoxycorticosterone slightly increased the fibrinolytic activity and the serum cholesterol as compared with Group 3 The clotting time the serum triglycerides and α lipoproteins in Group 6 did not differ significantly from those in Group 3 and the incidence of hepatic infarcts was 70 per cent as compared with 85 per cent in Group 3

In Group 7 in which only a single injection of heparin was administered the clotting time was the longest of all the groups and the triglycerides were the lowest The percentage of α lipoproteins was considerably increased at the expense of the α 2 lipoproteins and the peak of these α lipoproteins also migrated ahead of the albumin zone as in Group 6

*Table III. Influence of corticoids and heparin on various parameters and the production of*

| Group | Number of rats | Treatment | Duration of treatment (days) | Clot lysis* (%) | Plasma clotting time* (sec) |
|---|---|---|---|---|---|
| 1 | 17 | DIST | 1 | 36 ± 8 | 230 ± 10 |
| 2 | 17 | COL | 1 | 7 ± 4 | 241 ± 12 |
| 3 | 26 | DIST | 7 | 23 ± 5 | 241 ± 13 |
| 4 | 28 | COL | 7 | 15 ± 3 | 334 ± 22 |
| 5 | 14 | COL + EACA | 7 | 0.3 ± 0.2 | 330 ± 18 |
| 6 | 23 | DCA | 7 | 35 ± 6 | 263 ± 16 |
| 7 | 12 | Heparin | 1 | — | 463 ± 98 |

*Mean ± S.E.
†β- and pre-β lipoproteins.
*DIST*: Distilled water. *COL*: Hydrocortisone acetate. *DCA*: Desoxycorticosterone acetate.
Hydrocortisone (3 mg.) in 0.5 ml. of distilled water, or the same volume of distilled water alone, was injected subcutaneously once a
Thrombosis was induced by the intravenous injection of a *S. typhosa* lipopolysaccharide 2 hours after the last injection of hormone.
Group comparison—Plasma clotting time: 4, 5 and 7 vs 3, $p < 0.001$; 6 vs 3, $0.2 < p < 0.3$.
Lipoproteins: 4 and 7 vs 3, $p < 0.001$.
Triglycerides: 4 vs 3, $p < 0.05$.

incidence of thrombosis was reduced from 85 (Gr 3) to 16 per cent by the heparin treatment.

With regard to cardiac or renal infarcts, a combined incidence of 9 per cent was recorded in Groups 1 and 3; not one single renal or cardiac infarct was found in any of the other groups.

## Discussion

From these experiments it appears that the administration of ACTH or of glucocorticoids such as hydrocortisone or prednisolone for 3 to 7 days at the dosage used here not only markedly alleviates the mortality rate but also considerably reduces the incidence of hepatic thrombosis in the rat. These results were obtained over a period of several months, and those in Series III are the sum of several experiments. In this last series the results obtained were the most consistent, apparently owing to the long duration of the treatments (7 days). In addition, no cardiac or renal infarcts were detected in Series III except in groups injected with distilled water in lieu of the test substances.

The fact that a single administration of the glucocorticoids reduced the mortality rate is concordant with the known protective effect of corticoids on endotoxemic and other types of shock.[17,18] However, there was no effect on the incidence of thrombosis, a finding that constitutes another reason for differentiating in these as in previous experiments[14] between the mortality rate, which appears to be the result of shock, and the incidence of thrombosis.

This protective effect of corticoids against shock and thrombosis appears to be a prerogative of the glucocorticoids, at least for those examined here. Fluorohydrocortisone, a steroid possessing the two activities, was not so effective as hydrocortisone in protecting against thrombosis. In addition, desoxycorticosterone, a potent mineralocorticoid, consistently increased the mortality rate and did not reduce the incidence of thrombosis. However, further experiments appear to be needed in this regard, since it has been shown that aldosterone can prevent the endotoxin shock in monkeys[1] and mice.[22]

It has been reported that glucocorticoids increase the blood fibrinolytic activity in man[23] but also that ACTH decreases it in the rabbit.[24] Here, in the rat, the fibrinolytic activity was increased by desoxycorticosterone and decreased by hydrocortisone or prednisolone treatment. At any rate, the protection afforded by glucocorticoids against thrombosis could not

*hepatic vein thrombosis in rats*

| Cholesterol (mg %) | Triglycerides (mg %) | Lipoproteins (% ) | Hepatic infarct incidence (%) | Mortality (%) |
|---|---|---|---|---|
| 541 ± 80 | 133 ± 17 | 9 2 ± 0 8 | 76 | 64 |
| 515 ± 83 | 120 ± 10 | 10 5 ± 0 6 | 82 | 23 |
| 531 ± 61 | 128 ± 16 | 9 1 ± 1 1 | 85 | 54 |
| 575 ± 78 | 207 ± 37 | 22 1 ± 2 9† | 14 | 4 |
| — | — | — | 21 | 1 |
| 762 ± 110 | 133 ± 35 | 7 5 ± 2 8 | 70 | 100 |
| 641 ± 42 | 93 ± 5 | 72 8 ± 0 9† | 16 | 33 |

* EACA (Epsilon amino caproic acid) 2.5 mg/kg was given by stomach tube 2.5 hours before the injection of endotoxin and 1 hour after [illegible] (23 mg/kg subcutaneously) [illegible] rats fed the hyperlipemic diet for 11 weeks.

have been due to increased fibrinolysis since the administration of EACA which completely blocked the fibrinolytic activity was not able to inhibit the protective effect of the corticoids The present study also suggests that under certain conditions the fibrinolytic activity can be completely inhibited without necessarily increasing the risks of thrombosis

The present data confirm our previous findings [14] in that serum cholesterol and triglycerides are of little value in determining a thrombotic tendency at least in the rat Here the serum triglycerides were increased by cortisone treatment although the coagulability and the incidence of thrombosis was markedly decreased These experiments also confirm the close relationship already reported between the plasma clotting time in siliconized tubes [26] the percentage of α lipoproteins [14, 4] and the incidence of thrombosis

The effect of glucocorticoids on the production of hepatic thrombosis the clotting time and the lipoprotein electrophoretic mobility appears to be similar to that of heparin As previously shown [27] and confirmed here the administration of heparin markedly increases the clotting time and prevents the production of hepatic thrombosis in hyperlipemic rats It is also known that in man treatment with heparin induces the production of pre-α lipoproteins [8] It has been reported that a rise in the α lipoproteins cholesterol occurs in man after the administration of cortisone [29] although other workers have observed alterations in most atherogenic classes of lipoproteins in the rabbit [30] but not in man [31] However cortisone has been shown to increase the protamine titer in man [9] and to have a marked effect on the structure and the function of mast cells [27] potentially heparin liberators Although many more experiments are needed to verify such a hypothesis it is possible that glucocorticoids at certain dosages in rat and in man affect coagulation and thrombosis through liberation into the blood of heparin or heparin like substances

## Summary

Administration of ACTH or of glucocorticoids such as hydrocortisone or prednisolone to hyperlipemic rats for 3 to 7 days resulted in a marked protection against the shock and the large hepatic vein thrombosis induced by a *Salmonella typhosa* lipopolysaccharide By contrast a mineralocorticoid such as desoxycorticosterone increased the mortality rate and did not prevent the production of thrombosis A single injection of gluco-

corticoid did not affect the incidence of thrombosis although it markedly reduced the mortality rate.

The fibrinolytic activity was depressed by glucocorticoids but stimulated by desoxycorticosterone. In addition, EACA did not block the protective effects of glucocorticoids on thrombosis although it completely inhibited the fibrinolytic activity.

The preventive effects afforded by glucocorticoids could be related to a marked prolongation of the plasma clotting time and a considerable increase in the percentage of α-lipoproteins which migrated even ahead of the albumin zone on paper electrophoresis. These results were similar to those obtained after the administration of heparin.

We are particularly indebted to and wish to thank the following companies for the substances used in the present studies: Ciba of Canada for the desoxycorticosterone; Cyanamid of Canada for the EACA; Merck Sharp & Dohme for the hydrocortisone; and Pfizer of Canada for the prednisolone.

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# Case reports

## Reversible lupus-like illness induced by procainamide

*Berton L. London, M.D.**
*Detroit, Mich.*
*Irwin Pincus, M.D., F.A.C.P.***
*Los Angeles, Calif.*

The first case of lupus-like illness associated with procainamide therapy was reported by Ladd in 1962.[1] Ten additional cases have since been described.[2-4] The following case report is presented as an addition to the literature on an entity which may prove to occur with some frequency.

### Case report

B. P., a 50-year-old white man, was first treated with procainamide, 1.5 Gm. daily, in January 1962, for idiopathic paroxysmal atrial fibrillation of 4 years' duration. In April 1963, approximately 15 months after the onset of treatment, the patient began to experience migratory arthralgia involving multiple joints. There was no swelling of the joints, redness, or stiffness. The pain improved on salicylates but recurred intermittently over the next 8 months. Past medical history was negative except for transient asthma in childhood and two episodes of thrombophlebitis of the right leg. Family history was negative for rheumatoid arthritis, systemic lupus erythematosus, or other collagen diseases.

In December 1963 the patient was examined for the symptom of increasing and persistent arthralgia. He denied chest pain, rash, fever, or significant constitutional symptoms. Physical examination revealed a healthy-appearing man. The blood pressure was 120/80 mm. Hg. No skin eruptions or lesions were present. No significant lymphadenopathy was found. The heart was not enlarged. No thrill was palpable. Heart tones were normal, and no murmurs were heard. The apical rate was 60 with sinus rhythm. The lungs were clear to auscultation and percussion. The abdomen was soft and not tender. No organs or masses were palpable. No swelling of the joints, redness, heat, or limitation of motion was detected. Hemoglobin was 15.8 Gm., hematocrit was 49, sedimentation rate 22 mm. per hour. The white blood count was 6,400, with 63 per cent polymorphonuclear leukocytes, 6 per cent monocytes, 31 per cent lymphocytes. The blood Kahn test was negative, as was the latex test for rheumatoid arthritis. Urinalysis was negative for albumin, sugar, and cells. Serum uric acid determinations were 5.7 and 6.3 mg. per cent. The precipitation test for C-reactive protein was 1+. Serum electrophoresis showed a total protein of 7.1 Gm., with 74 per cent albumin, 3 per cent alpha 1, 9 per cent alpha 2, 8 per cent beta, and 6 per cent gamma globulin. The L.E. cell test was positive. X-ray films of the chest, hips, lumbosacral spine, pelvis, and feet were normal. The patient was treated with hydroxychloroquine sulfate, 400 mg. daily. Symptoms improved, but arthralgia recurred intermittently. L.E. cell tests remained positive in February and May 1964. In May, 1964, the relationship of procainamide to the lupus-like syndrome was suspected and the medication was discontinued. Within 4 weeks all symptoms in the joints subsided. In August, 1964, the L.E. cell test revealed less than 1 L.E. cell per 500 neutrophils. In December, 1964, the L.E. cell test was negative. The patient has been free of any symptoms in the joints for 16 months.

### Discussion

Various drugs have been implicated in precipitating lupus erythematosus or a lupus-like illness. The most frequent association has been with hydralazine. The occurrence of the hydralazine syndrome and its severity seem to be related to high dosage over long periods of time. Initial

Received for publication Feb. 10, 1966.
*Associate Attending Physician in Medicine, Sinai Hospital of Detroit; Clinical Instructor in Medicine, Wayne State University School of Medicine, Detroit, Mich. Address: 18310 M[illegible] Rd., Detroit, Mich.
**Associate Clinical Professor of Medicine and Physiology, University of Southern California, Los Angeles, Calif.

symptoms resemble early rheumatoid arthritis with pain and inflammation in the joints which disappear promptly on withdrawal of the drug. If therapy is continued, however, other manifestations of systemic lupus erythematosus occur, including fever, rash, arthritis, polyserositis, enlargement of lymph nodes and spleen, leukopenia, anemia, elevated serum globulins, and false positive serologic tests for syphilis. Positive L.E. cells are found only occasionally. Renal involvement is rarely if ever encountered.

Anticonvulsant therapy has also been reported to induce a lupus-like syndrome with a high frequency of positive L.E. cell tests. Reactions to trimethadione, diphenylhydantoin, and methylethylphenylhydantoin have been described. Although the clinical manifestations of systemic lupus erythematosus usually improved or disappeared when anticonvulsant therapy was terminated, serologic and serum protein abnormalities persisted in several of the cases reported. Two fatalities from the anticonvulsant lupus-like syndrome have been reported.

The relationship of drug therapy to lupus-like diseases remains obscure. Indeed, the three groups of drugs implicated seem to produce slightly different clinical syndromes. The hydralazine-induced lupus syndrome is dose related, completely reversible, and has a low incidence of positive L.E. cell tests. The reported cases of procainamide-induced syndrome do not seem to be related to dosage or duration of treatment, and all have had positive L.E. cell tests. In neither group has renal involvement been demonstrated. Several of the cases described in patients on anticonvulsant therapy showed evidence of clinical or serologic persistence of disease long after the drug had been discontinued. Two cases terminated fatally. One might speculate that in the cases of persistent or progressive disease, idiopathic systemic lupus erythematosus may have presented as a convulsive disorder, and anticonvulsant therapy was not a factor in the illness.

Several theories of pathogenesis have been considered. The concept that drugs may precipitate or unmask a latent lupus tendency is difficult to accept because of the prompt and complete recovery which follows withdrawal of the drugs in the hydralazine- and procainamide-induced disease. One would anticipate spontaneous clinical relapse in at least an occasional case. To our knowledge, this has not been described in the drug-induced syndrome.

Another possibility is that the drug activates a subclinical defect or deficiency in a fashion similar to that of primaquine and related drugs which precipitate anemia in patients with glucose-6-phosphate dehydrogenase deficiency. If this is the case, the underlying fault is yet to be identified.

Finally, it is possible that the syndrome described is a drug reaction which mimics but is not systemic lupus erythematosus. One can only stress that in the full-blown drug-induced disease the entity is indistinguishable from idiopathic systemic lupus erythematosus by present diagnostic methods.

## Summary and conclusions

An additional case of procainamide-induced lupus-like disease is described. Any patient on procainamide therapy who develops arthralgia should be studied for this syndrome. Several possible explanations of pathogenesis are considered. The relationship of drug to disease remains obscure.

## Addendum

After this article had been submitted for publication, one of the authors (B. L.) observed an additional case of procainamide-induced lupus syndrome. Mrs. I. D., a 53-year-old patient suffering from mitral stenosis secondary to rheumatic heart disease, developed pain in the joints and swelling of the fingers, wrists, and right elbow 1 month after being placed on procainamide therapy. The L.E. cell test was positive. All symptoms and abnormal findings disappeared within several weeks after cessation of procainamide therapy.


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# Idiopathic heart disease associated with pregnancy and the puerperium

*John B Johnson M D**
*Gulam Hussain Mir M D***
*Prospero Flores M D*
*Marion Mann M D*
*Washington D C*

Idiopathic heart disease associated with pregnancy and the puerperium is uncommon but has been reported sporadically in the American literature since 1937 The actual incidence of this disorder is unknown but it has been reported as 1 in 1 300 deliveries[1] and 1 in 4 000 obstetric admissions by different investigators The disorder involves primiparas as well as multiparas Many of the patients make complete clinical recovery The syndrome tends to recur with subsequent pregnancies The mortality rate is not accurately known but has been reported as being between 30 and 60 per cent[4,5] The etiology and pathogenesis are obscure The histopathologic data are limited Only 26 previous cases with histologic studies have been found in the literature to date

The purpose of this communication is to present a case of idiopathic heart disease associated with the puerperium in a 14 year old primipara the youngest patient so far reported The disorder in this instance was fatal within 6 months During this short period the heart rapidly increased in size from normal x ray silhouette on admission to a 440 gram heart at postmortem Careful diagnostic and cardiovascular studies were performed on this patient including electrocardiographic angiocardiographic and hemodynamic evaluations In addition pericardial myocardial biopsy under local anesthesia was performed early in the illness The comparative histologic myocardial changes at biopsy and later at postmortem are presented

## Case report

This 14 year-old Negro primigravida had always been in good health until the third trimester of pregnancy when she developed shortness of breath and dependent edema

Examination [illegible] the prenatal clinic at this time Nov 20 1961 revealed blood pressure of 144/92 mm Hg 1+ dependent edema and + albuminuria Her hematocrit was 33 per cent hemoglobin 8 15 Gm per cent The blood type was A Rh positive and the hemoglobin was AS She was hospitalized and treated with hydrochlorothiazide After 7 days of hospitalization the albumin[illegible] and edema had [illegible] and the blood pressure was 138/84 mm Hg During the next 6 weeks the urine and blood pressure remained normal but she gained 23 pounds

The second hospital admission occurred on Jan

From the Cardiovascular Laboratory Department of Medicine and the Department of Pathology Howard University College of Medicine and Freedmen's Hospital Washington D C
This study was supported in part by grant [illegible]
Service Department of Health Education and Welfare
Received for publication Feb 10 1964
Address Department of Medicine Howard University College of Medicine Washington D C
*Resident in Medicine (Cardiology)
**Resident Internal Medicine

11 1962 because of the development of generalized edema The admission blood pressure was 138/94 mm Hg Both lungs were clear The heart was not enlarged and was free of murmurs Her abdomen was unusually large because of the presence of twins and polyhydramnios On the second hospital day she developed a temperature of 100 6 F tachypnea (30 to 54 per minute) and a sinus tachycardia (110 to 140 per minute) The white blood cell count was 18 9 0 hematocrit 43 per cent blood urea nitrogen 29 mg per cent $CO_2$ combining power 53 volumes per cent fasting blood glucose 67 mg per cent serologic test for syphilis nonreactive and urinary albumin 4+ There was no evidence of disease of the respiratory tract other than a mild tonsillopharyngitis

With antibiotic therapy the patient s temperature became normal but she continued to have tachypnea and tachycardia until Jan 15 196 when she gave birth to twin boys following the induction of labor with Pitocin Her tal sign returned to normal soon after delivery and she was discharged 4 days post partum and was reported as doing well Three days later she was readmitted as an emergency case because of frontal headaches and incoherence In the Emergency Room she developed grand mal type convulsion and became temporarily comatose Physical examination on admission revealed a pulse of 1_2 respiration 40 blood pressure 140/90 mm Hg normal ocular fundi distended neck veins clear lung field tolic gallop rhythm but no cardiac murmurs or peripheral edema There were no neurologic deficit The cerebrospinal fluid and skull x ray film were normal The electroencephalogram was mildly abnormal with a left temporal focus Five days after admission she developed transient paresis of the right arm and leg and some blurring of vision

On Feb 5 1963 the fifteenth hospital day the patient complained of a nonproductive cough and developed pulmonary edema Auscultation showed an accentuated pulmonic second sound a diastolic gallop rhythm and a questionable pericardial friction rub A portable x ray film of the chest indicated cardiomegaly and massive pulmonary edema The increasing heart size and pulmonary changes are illustrated in Fig 1 A and B There was an 8 pound gain in weight during the 15 days of hospitalization She was rapidly digitalized and was also given antibiotics and steroids The cardiomegaly and tachycardia persisted A Grade 1 basal systolic murmur developed on the twentieth hospital day

*Significant laboratory data* SGOT SGPT ASO titer C reactive proteins serum calcium and electrolyte were all normal White blood cell count 7 800 hemoglobin 10 15 Gm per cent serum albumin 3 4 Gm per cent serum globulin 3 2 Gm per cent and the serum creatinine 2 4 mg per cent Lupus erythematosus preparations were negative

The questionable pericardial friction rub enlarging heart size and T wave changes suggested the possibility of pericarditis with effusion The clinical impression at this time was postpartum pericarditis of obscure etiology with pulmonary and cerebral emboli m

As the patient s condition stabilized right heart




Fig 1 A Supine anteroposterior position reveals heart and lungs to be essentially normal B Supine anteroposterior projection Cardiac silhouette is markedly enlarged Lungs demonstrate typical butterfly pattern of pulmonary edema

catheterization and angiocardiography were performed The hemodynamic data are shown in Table I These findings were interpreted as compatible with biventricular failure probably of the high output type Arterial oxygen unsaturation as slight The angiocardiogram showed consecutive visualization of the four cardiac chambers all of which were unusually capacious (Fig 2,A and B) The interventricular septum appeared to bulge into the right ventricle There was no evidence of pericardial effusion She was discharged on March 8 1963 to be readmitted later for pericardial and myocardial biopsies

She remained reasonably well compensated under ambulatory clinic therapy for heart failure On May

*Table I. Hemodynamic data obtained by right heart catheterization*

| *Parameter* | | *Patient at rest* |
|---|---|---|
| Cardiac index | (L/min/M²) | 3 2 |
| $O_2$ consumption | (c c /min /M²) | 158 |
| Blood $O_2$ saturation | (per cent) | |
| Arterial | | 93 |
| Mixed venous | | 58 |
| A V $O_2$ difference | (c c /L ) | 48 |
| Pressure (mm Hg) | | |
| Systemic | | 90/41 |
| Pulmonary artery | | 40/23 |
| Right ventricle | | |
| Systolic/diastolic | | 40/14 |
| End-diastolic/systolic × 100 | | 34 |
| Right atrium (mean) | | 14 |
| PC pulmonary artery wedge | | 21 |
| Vascular resistance (dyne sec cm ) | | |
| Pulmonary artery | | 571 |
| Pulmonary arteriolar | | 130 |
| Systemic | | 967 |

16 1962 pericardial and myocardial biopsies were performed under local anesthesia without compl ca tions Fifty milliliters of pericardial fluid was ob ta ned mears and cultures showed no bacteria The pericardial specimen showed con siderable thicken ing with acute fibrinous exudate in focal areas (*see below*) Sections from the myocardium revealed peri nuclear hydropic vacuolization of the myocardial fibers and the remaining sarcoplasm showed frag mentation and irregularity of staining (Fig 3 1) A specimen from a skeletal muscle showed perivascu l tis The patient was discharged in compensated cardiac state and under d gox n and chlorothiazide therapy

The fourth ho pital adm sion occurred on June 16 196 3 weeks after discharge w th a 3-day hi tory of omiting diarrhea and shortness of breath Pul was 170 per minute and blood pressure was 120/90 mm Hg The neck eins were greatly dis tended In addition basal pulmonary râles cardio-megaly a har h pan ystolic murmur at left sternal border d astolic gallop rhythm and a questionable friction rub were present The li er was palpable 1 fingerbreadth below the right co tal margin but was not tender There was no per pheral edema

*Laboratory data* Blood urea nitrogen 43 mg per ce it sodium 135 mEq /L pota ium 4 3 mEq /L chloride 84 mEq /L CO combining power 46 volumes per cent cholester ol 244 mg per cent and calcium 3 9 mEq /L The chest x y film showed persistent cardiomegaly The enous pres ure was 230 mm $H_2O$

The electrocard ogram showed low QRS voltage absent or in erted T w es in the l mb leads nd discordant T w ve in Leads V V (Fig 4) Serial




Fig 2 1 Angiocardiogram how dilated right atrium right entri le and pulmonary conus *B* Dilated left atrium and left entricle

electrocard ograms during the ent re illness were remarkable because of the chang ng lectrical axis wh ch term nated in axi of −90 degrees (Fig 5)

The pos bility of d gital toxication was sidered Digoxin was d scontinued w th subsequent cessation of the diarrhea When the drug was re umed se e al days later the patient aga began to ha loose bowel movements On the e hteenth hospital day she became extremely weak her pulse was thready and her blood pressure w not ob



Fig 3A Surgical biopsy of heart revealed degeneration of myocardial fibers. Note vacuoles within the sarcoplasm and pyknosis of many of the nuclei. Hematoxylin and eosin ×240

tainable. Serum electrolyte determinations performed the previous day showed the sodium to be 115 mEq per liter and the chloride 89 mEq per liter. In spite of the administration of intravenous fluid with electrolytes and vasopressor drugs the patient died on the nineteenth hospital day (July 4 1967)

At autopsy the *heart* weighed *440* grams. There were band like adhesions between pericardium and epicardium and many petechiae were scattered over the epicardium. A mural thrombus was attached in the apex and covered the anterior aspect of the left ventricular endocardium.

The progressive nature of this disorder and its fulminant course are well illustrated in the comparative histologic study of the postmortem sections of the heart and the biopsy sections taken 7 weeks earlier. The perinuclear vacuolization fragmentation and irregular staining of the muscle fibers in the biopsy specimens have been described above. In the postmortem specimen extensive destruction of muscle fiber was present with evidence of fibroblastic repair. There were many irregular foci of pale staining muscle fiber remnants consisting of sarcolemmal fragments pyknotic nuclei and necrosis (Fig 3B). Budding capillaries along with fibroblasts were profuse. Remnants of viable myocardial fibers within and adjacent to the areas of destruction showed evidence of hypertrophy but



Fig 3B The inflammatory cells chiefly lymphocytes are scattered among remnants of degenerating myocardial fiber. Hematoxylin and eosin ×180



Fig 3C Section through attached mural thrombus. A branch of papillary muscle became bed in the thrombus at the upper right. Focal calcification is seen at lower right. Hematoxylin and eosin ×60

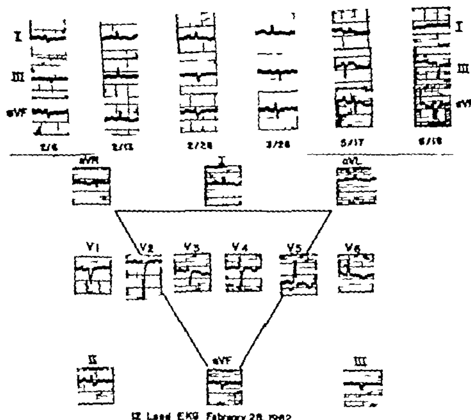
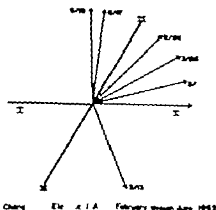



Fig. 4 Serial electrocardiograms demonstr ts gradual hange th QRS xi Low oltage l ft xi deviatio nd inversion of T in Lead I aVL V[5]-V




Chang Ele x l A February through June 1962

I g Diag ram ille trati of cha ges in th QRS xi f the l ect ocard gram

ere others sc tree f h t l gic ch ng The mural th omt er no ied b conta ed exte iva p ll ry nets ek n fbros t ue l some f of l rophi al he t (I + 3C)

The l er b l l 90 gram l w sever l lunaged bow ext d grees f ce t ld l

degenerat nd ne s The lu ign p ee and ki lnes we ested There wer n recog izable pulmonary embol The b n t exam ned

## Discussion

We have been able to document 26 autopsied cases of idiopathic heart disease associated with pregnancy and the puerperium to which is added the case of this report The 27 cases tabulated by age and previous pregnancy are listed in Table II Two significant features are apparent from this analysis first the dominant age group appears to be 30 to 39 years and second of the 22 cases for which data were available 62 per cent were multipara

It is to be noted from Table III that in 50 per cent of the fatal cases the clinical onset occurred prior to delivery or during the first week postpartum In nearly half of this group of fatal cases death occurred within 6 month

The most common clinical man

*Table II Distribution of autopsied cases by age and parity**

| *Age (yr) at onset* | *Cases* | | *Cases with previous pregnancies* |
|---|---|---|---|
| | *Number* | *Per cent* | |
| 14 19 | 5 | 18 5 | 0 |
| 20 29 | 4 | 14 8 | 4 |
| 30 39 | 13 | 48 2 | 10 |
| Age not stated | 5 | 18 5 | ? |
| Total | 27 | 100 0 | |

*Eighty [illegible] per cent of the cases studied were [illegible] patients [illegible] Negro [illegible] White [illegible] low [illegible] [illegible] and poor diet [illegible] [illegible] ted are related to the observations has been prev[illegible]d

*Table III The onset of symptoms and the duration of life after onset in autopsied cases**

| *Time of onset* | *Duration of life after onset* | | | *Total* |
|---|---|---|---|---|
| | *6 mo* | *6 12 mo* | *12 mo* | |
| Before labor | 4 | 1 | 3 | 8 |
| First week postpartum | 3 | 0 | 0 | 3 |
| ✓ Second to twentieth week postpartum | 3 | 1 | 6 | 10 |
| Total | 10 | 2 | 9 | 21 |

*Th[illegible] table does [illegible] include 5 cases which have [illegible] reported [illegible] [illegible] [illegible] [illegible] symptoms [illegible] d 9 years after the [illegible] last pregnancy with death 1½ years later

*Table IV Most common clinical manifestations in 22 autopsied cases**

| *Clinical manifestations* | *Number of cases* | *Percentage* |
|---|---|---|
| Dyspnea on exertion | 20 | 91 |
| Dependent edema without anasarca | 16 | 73 |
| Gallop rhythm | 14 | 64 |
| Murmurs | 14 | 64 |
| Abnormal ECGs | 11 | 50 |
| Orthopnea | 9 | 41 |
| History of hypertension (transient) | 8 | 36 |

*In 5 of the cases clinical manifestations were [illegible] individually reported[5]

tions tabulated in Table IV show that dyspnea on exertion dependent edema and gallop rhythm occur most frequently in this group of cases About one third of the patients also showed cough hemoptysis persistent tachycardia abdominal pains or history of hypertension at onset Other symptoms were infrequent in this series When the symptomatology was analyzed with reference to the initial symptoms dyspnea on exertion was present in 66 per cent of the cases Although cough and palpitations were not dominant in this series some authors have reported cough and palpitation to be more frequent in these cases than in ordinary cases of congestive heart failure

The hemodynamic studies in patients with postpartum heart disease have been extremely limited Other than the case reported herein we have found only one additional report on the hemodynamics in these patients[13] At the time of study our patient was in reasonable cardiac compensation although the massive cardiomegaly was evident The circulation time was 15 seconds As can be seen from Table I the end diastolic right ventricular pressure was elevated as was the pulmonary artery wedge pressure compatible with right and left ventricular failure The pulmonary vascular resistance was increased Nevertheless the cardiac output was within normal limits We interpreted this to be compatible with a high output type of biventricular failure These hemodynamic findings are in contrast to those reported by Pierce and associates In their cases the cardiac index was greatly reduced varying from 0 83 to 2 29 L /min /M[2] They also found an elevation in pulmonary arterial pressure in 2 cases but the pulmonary wedge pressure was not reported in their paper

Electrocardiographic studies in this group of 27 cases have been limited with reports having been listed in only 9 cases All cases showed low voltage complexes with flat or inverted T waves in most of the leads Sinus

tachycardia was present in 2 patients, atrial flutter in 1, and left bundle branch block in 2, and in the case which we report a rapidly changing electrical axis from 0 to −90 degrees in a 4 month period (Figs. 4 and 5).

### Cardiomegaly and mural thrombi

The gross and microscopic pathologies of published cases of postpartum heart disease have been analyzed and compared with the findings in the present case. Cardiomegaly in terms of heart weight was surprisingly great. Of the 24 cases in which the heart weight was reported, in only 2 did the heart weigh less than 300 grams. In 18 cases, 75 per cent, the heart weights were between 350 and 650 grams. Dilated heart chambers were commonly mentioned. In our case, at least, the greatly enlarged chambers were not merely a terminal event since they were demonstrated by angiocardiography during the early stage of illness. Mural thrombi of the heart were very common, being present in 18 of 27 cases (67 per cent). The thrombus was in the left ventricle alone in 8 cases and in multiple chambers in 9 cases, usually including the right ventricle. No cases showed coronary occlusion.

### Histopathology

The histopathologic findings which other authors have described comprise degenerative, inflammatory, and reparative changes which reflect the combined effect of hypoxia, focal ischemia, and mechanical or other stresses within the myocardium. The degenerative changes consisted of cloudy swelling, fragmentation, loss of cross striations, and irregular staining of muscle fibers along with pyknosis, hyperchromatism, and karyolysis of nuclei. Hemorrhagic necrosis was occasionally reported. Cellular infiltration consisted mostly of lymphocytes, mononuclear cells with occasional plasma cells, and macrophages. Endocardial thickening and fibrosis were reported in 50 per cent of patients (Fig. 6).

The progressive nature of the myocardial lesion is suggested by the presence of reparative and degenerative changes in the same microscopic field. The rapidity of the progression, however, is best shown in the histologic picture of the myocardial biopsy specimen from our patient as compared with the histologic picture of the myocardium 2 months later at postmortem (Fig. 3).

The fibrinous pericarditis present in the biopsy specimen in our case is unexplained. There were no histologic changes in the myocardium or elsewhere suggesting active rheumatic pancarditis or lupus erythematosus. Fibrinous pericarditis was not noted in postmortem examination in any of the 27 cases.

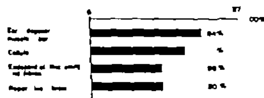


Fig. 6. Histopathologic changes in the myocardium in 27 fatal cases of postpartum heart disease.


### Summary

The case of a 14 year old primigravida in whom idiopathic heart disease associated with pregnancy and the puerperium proved fatal 6 months postpartum is presented. Hemodynamic and angiocardiographic studies revealed data compatible with right and left ventricular failure of the high output type and enlargement of all cardiac chambers. The QRS axis of the electrocardiogram showed progressive left axis deviation which seemed to parallel the severity of the disease.

Comparative histologic studies of the myocardial biopsy specimen and 2 months later of the heart postmortem showed evidence of a rapidly progressive, widespread degenerative and reparative process in the myocardium.

A review of the American literature reveals only 27 autopsied cases, including our case, and no previous myocardial biopsies of this disease of obscure etiology.

We have analyzed the 27 autopsied cases with reference to clinical manifestations, electrocardiographic changes, cardiac hypertrophy, mural thrombi, and histopathology, and most of these cases show striking similarity as reported by different investigators.

Idiopathic heart disease associated with

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| 20-29 | 4 | 14.8 | 4 |
| 30-39 | 13 | 48.2 | 10 |
| Age not stated | 5 | 18.5 | ? |
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*[illegible] Negro [illegible] White [illegible] stated [illegible] observation [illegible] been [illegible]

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Fig. 6. Histopathologic changes in the myocardium in 27 fatal cases of postpartum heart disease.

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Idiopathic heart disease

pregnancy and the puerperium continues to remain an enigma with reference to etiology and pathogenesis

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# Electrocardiogram in ventricular rupture after myocardial infarction

## Case report

*David E. Morton, M.D.**
*John W. Gardner, M.D.*
*George E. McKinnon, M.D.*
*Pueblo, Colo.*

The odds against recording an electrocardiogram at the time of rupture of the myocardium must be very high. A review of the English literature and consultation with several cardiologists have failed to turn up a single report of such a finding. An electrocardiogram was recorded on a patient who complained of severe precordial pain on the fifth day after a diaphragmatic myocardial infarction, and by mere chance the tracing was made at the time of myocardial rupture and the rather sudden death of the patient. Many of the findings were those previously described in the dying heart.[1-4]

### Case report

T. B., a 54-year-old white woman, was admitted to St. Mary Corwin Hospital on April 23, 1964, complaining of severe anterior chest pain with radiation into the left arm; the pain had begun 2 hours previously while she was attending her brother's funeral, and was not relieved by three nitroglycerin tablets. She had a past history of treatment for labile hypertension (140-180/76-110 mm. Hg) since 1959, an episode of coronary insufficiency in 1960, and severe coronary insufficiency or possibly myocardial infarction in February, 1964. She had been treated for ankle edema with diuretics since 1960. She had had typical angina pectoris intermittently for several months prior to her current admission, and she was on bishydroxycoumarin. She had a history of recurrent thrombophlebitis of both legs, an old cholecystectomy, chronic rheumatoid arthritis, and an old esophageal hiatus hernia.

Physical examination revealed a slightly obe[se], very apprehensive woman of 54 years. She w[as] overbreathing and exhibiting carpopedal spasm. The respirations were 30, pulse 110 and regular, blood pressure 160/90 mm. Hg, and temperature 99 F. There was xanthelasma of the eyelid. She wa[s] slightly flushed and slightly cyanotic. The chest was mildly emphysematous with a few crackling râles scattered throughout both lung fields. The heart was somewhat enlarged to the left. A[2] wa[s] louder than P[2]. No murmurs or pericardial friction rub were heard. There were small varicose veins o[f] the legs with signs of old chronic thrombophlebitis and slight pitting edema of both legs. There wa[s] mild generalized rheumatoid arthritis.

The prothrombin time was 27 seconds on admission; the blood count and urine were normal except for a trace of albumin in the latter. The initial SGOT was 24 units; 12 hours after admission it was 44 units, and 24 hours after admission it was 76 units. The cholesterol was 420 mg. per cent 3 days after admission. Chest x-ray films were normal ex[cept] for a retrocardiac density which was thought to be an esophageal hiatus herni[a].

A[n] [illegible] electrocardiogram recorded the [day of admission] showed sinus tachycardia and left ve[ntricular] ... and was suggestive of an early diaphragmatic myocardial infarction with elevated S-T segments in Leads II, III, and aV[F] (Fig. 1). The ECG recorded

From the Departm[ent] of I[nt]ernal Medicine and the Department of Pathology, St. Mary Corwin Hospital, Pueblo, Colo.
Received for publication Feb. 10, 1966.
*Address: 19 [...] Pueblo, Colo. 81004

the day after admission revealed typical changes of a acute diaphragmatic myocardial infarction with Leads III and aVF showing Q waves elevated S T segments and inverted T waves Inverted T waves in the precordial leads also suggested some antero lateral myocardial ischemia (Fig 2)

The patient was given oxygen meperidine papaverine and trichlormethiazide Bishydroxycoumarin was continued She responded well to treatment and her blood pressure during the next few days remained around 130/80 mm Hg Her chest pain disappeared and she felt well On the evening of the fifth day after admission she suddenly complained of anterior chest pain and within 5 minutes was unresponsive pulseless without blood pressure and gasping She was given oxygen and metaraminol but failed to respond and died within 10 minutes An ECG was recorded just after the patient lapsed into shock and coma and was run continuously until there was no further heart action It will be discussed below The clinical impression was diaphragmatic myocardial infarction due to coronary thrombosis and arteriosclerotic heart disease with rupture of the left ventricle and pericardial tamponade

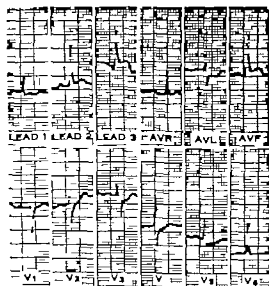



Fig 1 Electrocardiogram taken about 2 hours after the symptoms of myocardial infarction had begun to suggest an early diaphragmatic myocardial infarction

The terminal tracing (Fig 3) showed ventricular fibrillation in Lead I then resumption of normal sinus rhythm in subsequent leads with a marked intraventricular conduction defect the QRS complexes having measured about 0 20 second In the precordial leads there was a progressive decrease in amplitude of the QRS complexes down to almost nothing The final continuous strip (Lead $V_4$) showed a marked first degree heart block (P R interval of about 0 40 second) which developed in Lead $V_4$ with continued very low amplitude of the QRS complexes Then the P wave dropped out or changed in configuration Definite P waves then reappeared with a marked first degree A V block Then the QRS waves stopped and only the P waves remained The QRS waves then returned with marked first degree heart block Some QRS complexes were followed by an inverted wave of uncertain origin The QRS waves then came and went intermittently Then only the P waves remained and finally they disappeared leaving only a straight line which indicated the end of all cardiac electrical activity

*Autopsy findings* The pericardial sac was distended with 400 ml of partly clotted blood The heart weighed 370 grams The right ventricular

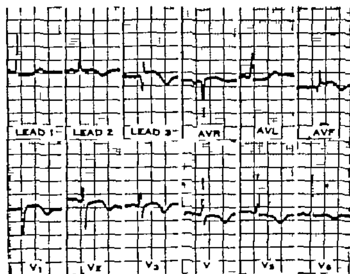



Fig 2 Electrocardiogram taken the day after the onset of myocardial infarction shows the typical picture of an evolving diaphragmatic myocardial infarction

chamber was about normal in size. The left ventricular chamber was dilated. Both coronary artery orifices were wide. The right main coronary artery showed moderate arteriosclerosis. It was completely occluded by what appeared to be a fairly fresh dark red thrombus at a level about 3 cm. out from the orifice. The left anterior descending coronary artery was moderately narrowed by arteriosclerosis. The left circumflex artery also showed moderate narrowing by arteriosclerosis. No occlusion was found in this vessel but it appeared to be attenuated with only a few small branches supplying the lateral portion of the left ventricle and it appeared that the posterior portion was supplied predominantly by the right coronary artery. An infarcted area with light yellowish tan coloration and softer in consistency than the adjacent myocardium occupied a region in the posterior basilar left ventricular wall about 5.5 cm. in greatest diameter. On section the necrosis appeared to involve the posterior basilar wall of the left ventricle and the posterior basilar portion of the interventricular septum. In the septum it extended anteriorly all the way to the thin portion of the septum beneath the tricuspid ring. Perforation of the myocardium had occurred and an irregular hole extended between the chamber of the left ventricle and the pericardial sac. There was some dissection across the septum into the posterior muscular wall of the right ventricle as well but the hole which led to the pericardial cavity was situated to the left of the septum. In the epicardium of the heart over its posterior basilar surface there was a hematoma about 1 cm. thick and 4 cm. in diameter (Figs. 4 and 5).

All of the sections of the coronary arteries taken for microscopic examination showed arteriosclerosis. The branches from the left artery were narrowed to a variable extent by this. Some such cross sections revealed a lumen only about one half of the usual size. Sections of the right coronary artery showed in addition to the arteriosclerosis thrombus material filling the lumen. At some levels the thrombus material appeared to be of two different ages with organization apparent at the edge of the older material and with the remainder of the lumen filled with the fresher thrombus material.

Sections from the posterior basilar left ventricle and interventricular septum revealed large patches showing changes of subacute myocardial infarction. In these areas the myocardial cells had for the most part disappeared and the patches were made up of loose relatively hypervascular granulation tissue with beginning scar formation. Around the edges of

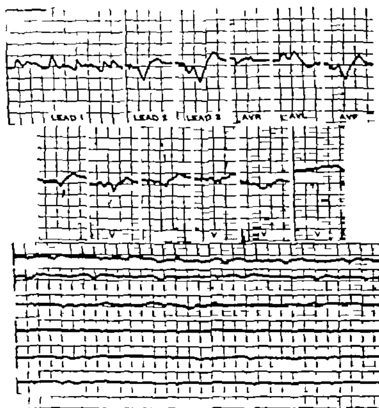



Fig. 3. Electrocardiogram taken on the fifth day after the onset of myocardial infarction depicts the events just after rupture of the posterior basilar portion of the left ventricle and the terminal electrocardiographic changes in the dying heart. See text for details.




Fig 4 Heart at necropsy showing (1) an epicardial hematoma and (2) hemorrhagic necrosis at the edge of the rupture tract in the posterior basilar portion of the interventricular septum



Fig 5 Heart looking at the septal face of the left ventricle showing a probe passing through the rupture in the posterior basilar wall of the left ventricle

these patches of subacute infarction there were a few patches of more acute necrosis where muddy pink staining myocardial cells were visible Most of these had lost their nucleus and striations At the edges of these more acute necroses were accumulations of polymorphonuclear leukocytes

Step block sections beginning on the ridge between the foramen ovale and the orifice of the coronary sinus in the right atrium and extending down across the atrioventricular junction into the basilar interventricular septum were made to show the conducting system[4] The necrosis of the septal myocardium extended nearly but not all of the way through to the left endocardial face of the septum On the right side of the septum necrosis accompanied by inflammatory cells was demonstrated up to and including the endocardial surface Fig 6 shows involvement of the subendocardial specialized muscle of the conduction system

Three different sections taken through the site of myocardial rupture revealed hemorrhage and fibrin clinging to the edges of the tract The rupture appeared to have occurred through the areas of subacute infarction The hemorrhage in the myocardial layer was limited to a relatively narrow zone of muscle on either side of the tract of rupture In the epicardial fat however it spread out over a broad flat zone of considerable size

## Discussion

A 54 year old white woman with hypercholesterolemia developed a diaphragmatic myocardial infarction despite previous adequate anticoagulation At some time before the terminal episode the myocardial infarction extended from the posterior left ventricular wall into the interventricular septum causing the development of the marked intraventricular conduction defect seen on the final tracing (Fig 3) The gross pathologic findings indicated posterior septal involvement as far forward as the thin portion of the interventricular septum beneath the tricuspid ring It was not possible to classify definitely the type of intraventricular conduction defect on the terminal electrocardiogram and microscopic examination revealed that both the right and left bundle tissues were damaged especially the right

The rapidly decreasing amplitude of the QRS complexes from 5 to 1.5 mm in Leads aVL, aVF and the precordial leads may have been associated with the dying heart however this has not been reported generally in the literature A more likely explanation may be that the rapidly developing hemopericardium which followed the left ventricular rupture produced this picture

The final continuous strip (Lead $V_1$) recorded the terminal events in the dying heart with first degree heart block intraventricular conduction defect intermittent cessation of ventricular complexes and

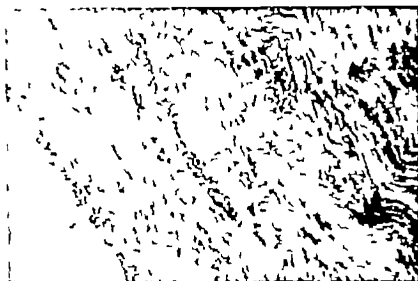


Fig. 6. Microscopic section through the right half of the interventricular septum with the right ventricular cavity on the left of the figure. Myocardial necrosis is shown on the right with leukocytic infiltration extending to the endocardium on the left. Involvement of the long subendocardial Purkinje fibers is apparent. Magnification ×80.

finally, disappearance of the P waves with permanent and total cessation of electrical activity in the heart.

## Summary

The case of a 54 year old white woman is presented in which an electrocardiogram was recorded at or shortly after the time of rupture of the left ventricle on the fifth day after a diaphragmatic myocardial infarction. The chief features of the terminal electrocardiogram were transient ventricular fibrillation, marked intraventricular conduction defect, rapidly decreasing amplitude of the QRS waves, development of first degree atrioventricular block, intermittent cessation of ventricular (QRS) complexes, and finally, disappearance of atrial activity (cessation of P waves). Autopsy findings gave an excellent correlation with clinical and electrocardiographic findings. As far as can be determined, there has been no previous report of electrocardiographic findings at the time of ventricular rupture. Most of the changes described on the terminal electrocardiogram have been described before in the dying heart and are not diagnostic of myocardial rupture. However, the decreasing amplitude of the QRS complexes may have indicated developing hemopericardium secondary to ventricular rupture.

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# Clinical pathologic conference

*C H Stuart Harris CBE MD FRCP**
*T J Bayley MB ChB MRCP*
*Donald Heath MD PhD MRCP***
*Birmingham England*

## Clinical abstract

DR BAYLEY The patient was a 67 year-old housewife who had suffered from arthritis since the age of 16 years This affected her hands wrists knees elbows shoulders ankles and hips in order of decreasing severity By 1963 the right wrist had become ankylosed There was ulnar deviation of both hands There was fixed flexion of both elbows (left 10 degrees of movement right 10 degrees) and knees (left 5 degrees of movement right 10 degrees) The feet showed early fibular deviation and there was fixed extension of the right great toe There were nodules about both elbows For 6 years she had been treated with a drug but the dosage of this was reduced in 1961

When she was 40 years old a swelling on one of her left ribs had been removed Two years later another swelling from the same site had been removed When she was 58 years old a radiograph of the chest revealed a shadow in the left hemithorax a mass was subsequently removed from the left lung

She was admitted to the hospital on Oct 6 1963 at the age of 64 years with complaints of a throbbing pain in her left loin She said that for 18 months she had been able to feel a lump on the left side of her abdomen On examination it was confirmed that she had a mobile ovoid mass 5 by 4 by 3 inches in size in the left hypochondrium This mass appeared to be firm and smooth with well-defined margins and the skin was freely movable over it It was not tender there was no evidence of pulsation or fluctuation in it and there was no redness or heat associated with it On Oct 17 1963 this mass was removed at laparotomy At the time of operation a hiatus hernia was found She was discharged from the hospital on Oct 27 1963

She was rehospitalized on May 1 1964 because of increasing pain in her legs There was evidence of sensory impairment in both feet together with areas of hyperesthesia No abnormal clinical signs were found in the chest or abdomen Her systemic blood pressure was 160/95 mm Hg Her radial pulse rate was regular at 94 per minute There was bluish discoloration of the toes There was no evidence of anemia or lymphadenopathy She was discharged on June 5 1964

She was rehospitalized on Oct 25 1965 with complaints that she had been increasingly breathless for 3 months For 2 weeks she had had rapidly increasing swelling of the legs and abdomen On examination she was very dyspneic even when talking She had Cushingoid features and purpuric spots On examination the jugular venous pressure was raised to the angle of the jaw There was massive edema of both legs and sacral pad There was free fluid in the peritoneal cavity There was a rapid irregular tachycardia On auscultation no murmurs were heard The systemic blood pressure was 130/80 mm Hg The trachea was central There was diminished respiratory movement over the left side of the chest There was dullness to percussion at the left base posteriorly Breath sounds were much diminished in that area On October 27 a left pleural tap was performed but only a few milliliters of fluid were aspirated She remained very breathless and edematous Further taps were attempted on October 30 and November 5 but on neither occasion was fluid obtained She showed no improvement despite *intensive treatment* She had no diuresis and became more and more breathless She became unconscious on November 12 and died 2 days later

The results of laboratory investigations are given in Table I

## Discussion

PROF STUART HARRIS This somewhat unusual patient had polyarthritis for 51 years died with the signs and symptoms of congestive heart failure and underwent

From the Medical School University of Birmingham Birmingham England
Received for publication May 25 1966
*Sir George Frankl[?] Professor of Medicine University of Sheffield
**Address Department of Pathology Medical School University of Birmingham Birmingham 15 England

*Table I. Laboratory investigations*

Hemoglobin 71 per cent (May 30 1964) 75 per cent (Nov 12 1965)
White cell count (per cubic millimeter) 9 800 (May 30 1964) 21 400 (Nov 12 1965)
White cell differentials (per cent)
  May 30 1964—Polymorphs 87 eosinophils 1 monocytes 2 lymphocytes 10
  Nov 12 1965—Polymorphs 87 eosinophils 1 monocytes 2 lymphocytes 10
Blood urea (mg per 100 ml ) varied between 32 and 65 between Oct 27 1965 and Nov 6 1965
Serum albumin (grams per 100 ml ) varied between 2 8 and 3 0 between Oct 7 1963 and Nov 8 1965
Serum globulin (grams per 100 ml ) varied between 2 6 and 3 4 between Oct 7 1963 and Nov 8 1965
Liver function tests (Oct 26 1965)
  Bilirubin 0 9 mg per 100 ml
  Alkaline phosphatase 9 9 units per 100 ml
  Thymol turbidity 1 unit
CSF (May 1 1964) pressure was 185 mm $H_2O$ Free rise and fall
Wassermann reaction (Oct 14 1963) was negative
Pleural fluid (Oct 27 1965)
  No pus cells organisms tubercle bacilli or malignant cells
  No growth of organisms on culture
Barium meal (Oct 11 1963)
  Very small sliding hiatal hernia with gastro-esophageal reflex
Blood gases (Oct 26 1965)
  pH 7 49 $pCO_2$ 40 mm Hg standard $HCO_3$ 29 mEq /L

four surgical operations Since the nature of these operations is not clear at the present I intend to consider first of all the arthritis then the terminal illness and finally the masses in the chest and abdomen that necessitated surgical treatment

The age of the patient at the time of onset of the arthritis her sex the order of importance of involvement of the joints and the fact that the maximum severity of the arthritis occurred in the hands and wrists leads me to the conclusion that we are dealing here with rheumatoid arthritis The extreme limitation of movement reported in the joints suggests that fibrous and possibly bony ankylosis had taken place There is no other disease that can last a lifetime cripple the patient and yet not lead to death excluding that is diseases like psoriatic arthropathy and ankylosing spondylitis Neither of these latter diseases would really fit the bill in the present case

In the last 2 years of her life this patient had complications in the abdomen nervous system and cardiovascular system All of these are far from common in rheumatoid arthritis In May 1964 she had increasing pain in the legs with sensory impairment and hyperesthesia in the feet This appears to have been a peripheral neuropathy and its development in rheumatoid arthritis is highly significant Even if my own references had let me down the Editor of the *British Medical Journal* published on April 23 of this year a clinicopathologic conference held at the Post Graduate Medical School Hammersmith on a patient who also had rheumatoid arthritis and a peripheral neuropathy [1] There are also a number of papers published on the subject All agree that such involvement of the nerves indicates the development of an arteritis [2] In some ways it resembles polyarteritis nodosa although there may be some obliterative changes and it brings with it a bad prognosis Such patients have long standing rheumatoid arthritis as in this case they possess subcutaneous nodules and they have high titers of the Rose Waaler differential agglutinin or rheumatoid factor The serum electrophoretic pattern is a little different from that of ordinary rheumatoid arthritis They may or may not have received long term treatment with steroids I note that the present patient had a long course of therapy and that the dosage of the drug was reduced in 1964 the assumption is that she had been receiving steroids Before we proceed let me see a radiograph of the hands and know the titer of the Rose Waaler test At this stage it might be a good idea to ask you whether lupus erythematosus cells were ever found in this woman

DR BAYLEY The latex slide test for rheumatoid arthritis was positive The Rose Waaler test was also positive to a titer of 128 No lupus erythematosus cells were seen

PROF STUART HARRIS I would regard the titer of the Rose Waaler test as being high The radiograph of the hands and wrists (Fig 1) shows marked destructive changes in the interphalangeal and metacarpophalangeal joints The bones




Fig 1 Radiograph of hand

some rarefaction with cystic change which may have been of importance at an earlier stage of the disease but which is of no value now in the differential diagnosis between rheumatoid arthritis gout and the bone lesions of sarcoid The carpus has undergone fusion All of these changes are consistent with rheumatoid arthritis and I think that bony ankylosis has occurred in this case

We are not told of the subsequent history of the peripheral neuritis It seems to be likely that she would have shown an arteritis in relation to the nerves themselves In the paper of Hart and Golding[2] they give a description of a series of cases of polyarthritis with peripheral neuritis Some of these patients died in cardiac failure gradually in some cases and suddenly in others

Now as to the nature of the terminal illness In October 1965 she had dyspnea swelling of the legs an elevated jugular venous pressure and free fluid in the peritoneal cavity All of this appears to be right heart failure with edema She had purpura She had an irregular cardiac rhythm which I presume was atrial fibrillation and I note that her systemic blood pressure had fallen from 160/95 mm Hg in 1964 to 130 80 mm Hg a year later All of these changes might be explained by ischemic changes or even a myocardial infarction or less likely by the endocarditis that may complicate rheumatoid disease (At this point the ECG was shown )

Well this ECG confirms that this patient had atrial fibrillation There is a feeble voltage in the limb leads I see no evidence of a recent infarction although there are minor changes consistent with ischemia The swing of the QRS complexes is poor and this might indicate damping down by free fluid in the pericardium associated with pericarditis All in all however there are no major features of intrinsic heart disease in this ECG

DR BAYLEY The only other abnormality besides the atrial fibrillation that you have already commented on which was noted at the time was a digitalis effect

PROF STUART HARRIS She had purpura This is not common in congestive cardiac failure but may occur in uremia However the levels of blood urea recorded are only slightly elevated such as might be found in congestive failure and do not suggest that she has renal failure secondary to arteritis of the renal arteries Also I note that there are no red cells protein or casts in the urine

It would seem that we shall have to look elsewhere for the basis of her terminal illness. This brings us to a consideration of the nature of her lung disease. The description of dullness and diminished breath sounds on the left side of the chest suggests that she had a pleural effusion, but I note that only a few milliliters of fluid were obtained by pleural tap. Of course, you can have such an effusion in rheumatoid disease if the lung is affected by interstitial fibrosis or honeycomb change, but I do not think that such lesions were present in this case. Let us see a chest radiograph. (This was shown; see Fig. 2.) Well, there is a large opacity in the left side of the chest. This looks more like an intrapulmonary mass than an effusion to me, and I think that it is likely that we shall have to go back into the history to see whether this is related to the masses in the thorax which were removed previously. I note from the radiograph that the eighth left rib has been removed.

A swelling of this rib was removed when she was 40 years old. Later this mass recurred in the left lung. Subsequently, a mass developed in the abdomen. Well, this rib tumor may have been a giant cell tumor or a chondroma or even possibly an eosinophilic granuloma of bone. However, since the surgeons clearly removed a discrete mass from the left lung, the diagnosis of eosinophilic granuloma is unlikely, because this would be associated with a more diffuse lesion in the lung. For this reason, too, I think that it is unlikely that we are dealing with a diffuse fibrosis of the lung. I favor the idea that we are dealing here with a locally invasive mass that began in the rib. Do we have a radiograph of the rib or chest taken when she was 58 years old? (A radiograph of the chest was shown.) Well, this shows a locally invasive mass without diffuse pulmonary change. Before we decide on the nature of this, I think that we must consider the abdominal mass. From its description I would say that this could be a localized mass in the peritoneal cavity, possibly a hydatid cyst or a metastasis from the mass in the chest, an enlarged kidney, or an enlarged spleen. However, the description is not really consistent with an enlarged kidney, and the mention of pain caused by the abdominal mass is not characteristic of splenomegaly, unless there has been some acute change in the spleen, such as an infarct, a subcapsular hematoma, such as might follow an arteritis, or even torsion.

DR HEATH We examined this abdominal mass in the pathology laboratory and found that it consisted of plump cartilage cells, some of which were binuclear, with a great deal of myxomatous basophilic matrix. The cartilage cells were arranged haphazardly. The appearances were reported as being consistent with a metastasis from a chondrosarcoma.

PROF STUART HARRIS This explains the mass in the chest very well. Clearly, the original tumors removed were chondromas. I imagine that malignant change took place, and that they recurred locally in the lung, probably by direct spread. Subsequently, there was more distant spread by blood or lymphatics.

DR WHITTLE Was it possible that this woman had some form of dyschondroplasia, such as Ollier's disease, with secondary sarcomatous change occurring in later life? This would explain the widespread distribution of sarcoma.

PROF STUART HARRIS I agree that she has extensive pathology, but we must remember that she lived to the age of 67 years. I am more impressed by the long periods of time in which there was no apparent development of her pathology



Fig 2 Radiograph of chest taken on Nov 4 19[illegible]5

I think that it is likely that the spread of sarcoma was from her single rib tumor and not on the basis of malignant change on a diffuse bone pathology like Ollier s disease

DR SMITH Is it possible that the peripheral neuritis was some sort of neoplastic neuropathy something akin to carcinomatous neuropathy?

PROF STUART HARRIS It is a possibility but I know of no specific association between chondrosarcoma and neuropathy

DR HEATH At autopsy this woman showed the typical features of rheumatoid arthritis The right atrium of the heart was enlarged and infiltrating its muscular wall was a tumor which measured 5 by 4 cm On cut section (Fig 3) it extended to within 3 cm of the edge of the fossa ovalis On sectioning the tumor was whitish in color and contained many cysts A glairy white fluid extruded from it and it was consistent in appearance with being a metastasis of chondrosarcoma The lower pole of the tumor had ulcerated into the cavity of the right atrium forming a papilliferous mass and superimposed on this was much antemortem thrombus At first sight the appearances were reminiscent of an atrial myxoma but the solid cartilaginous appearance revealed its true nature which was subsequently confirmed on histologic examination

The right ventricle was hypertrophied this chamber was 5 mm thick and weighed 71 grams This was subsequently found to be due to tumor emboli in the lungs many muscular pulmonary arteries were occluded by fragments of chondrosarcoma which had broken off from the friable tumor mass in the right atrium (Fig 4)

There were two deposits of chondrosarcoma in the left lung One of these was 5 cm in diameter and was situated on the anterior edge of the upper portion of the left lower lobe (Fig 5) On section this



Fig 3 Chondrosarcoma infiltrating the wall of the right atrium



Fig 4 Tumor emboli (*indicated by arrows*) in two muscular pulmonary arteries (Hematoxylin and eosin ×250 )



Fig 5 The smaller metastasis in the left lower lobe shown in section

was white in color and contained many small cysts from which a clear glairy fluid could be extruded (Fig 5) There was a second larger tumor mass in the base of the left lower lobe This was the size of a melon and on cut section showed solid white areas of chondrosarcoma hemorrhage and necrosis (Fig 6)

On histologic examination the appearances were typical of chondrosarcoma In some areas cartilage cells were readily identifiable although they were haphazardly arranged and some were of bizarre appearance (Fig 7) Most had plump nuclei and some giant cell forms were seen Some cells were binuclear Mitotic activity strangely enough was not much in evidence Between these islands of neoplastic cartilage cells there was much basophilic matrix showing pronounced myxomatous change (Fig 8) Fibrous strands coursed throughout the tumor tissue (Fig 8)

According to authorities such as Lichtenstein and Jaffe[1] when one is deciding the degree of malignancy of cartilaginous tumors the type and distribution of changes in the tumor matrix is unimportant The important indications of malignancy are the plump and multinuclear nature of the tumor nuclei together with the presence of giant cell forms Such criteria of malignancy were certainly present in this case

This case of chondrosarcoma is classic in showing the onset of the tumor in middle life rather than in early life as in osteogenic sarcoma Furthermore the long drawn out clinical history of local recurrence before the final widespread dissemination of metastases is characteristic this again contrasts sharply with the behavior of osteogenic sarcoma The distribution of the metastases to the heart and lungs is also very typical Lichtenstein and Jaffe[1] point out that the presence of severe respiratory and cardiac symptoms in the terminal illness of a patient with chondrosarcoma may well be a clinical indication of intravascular spread of the tumor with extension to the heart and lungs

I might add that there was no evidence of systemic rheumatoid disease in the form of rheumatoid aortitis or arteritis or of honeycomb lung There was also no evidence of Ollier's disease Do you think that the metastasis of sarcoma in the wall of the right atrium was the cause of the atrial fibrillation?

PROF STUART HARRIS Yes I do particularly since the tumor had infiltrated the muscle coat This case certainly shows that in elderly people we must reject the old aphorism that you must explain all the signs and symptoms on the basis of one pathology Clearly we need a new aphorism that there are almost certainly



Fig 6 The larger metastasis in the left lower lobe shown in section



Fig 7 Histologic section of the chondrosarcoma in the wall of the right atrium Note the plump neoplastic cartilage cell (Hematoxylin and eosin X150)

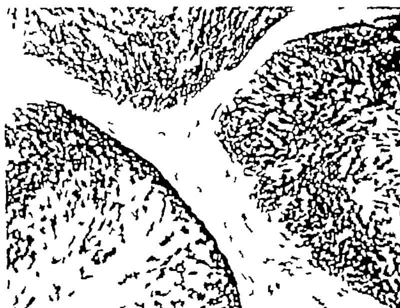


Fig 8 Histologic section of the chondrosarcoma in the wall of the right atrium showing islands of myxomatous matrix separated by strands of fibrous tissue (Hematoxylin and eosin ×60)

at least two pathologic processes present by the time one reaches the age of 67 years!

DR HEATH I think that this case supports the view held by some authorities that if malignancy in a cartilaginous tumor is suspected early resection should be adequate to prevent local recurrence and final widespread dissemination of metastases such as occurred here

PROF ORR Would you on the other hand agree that ideas on malignancy in chondrosarcomas vary a great deal according to the authority whom you are quoting? My general impression is that we see many cartilaginous tumors in cases in which the degree of malignancy is in doubt Under these circumstances should our report encourage the surgeons to undertake mutilating operations?

DR HEATH Lichtenstein and Jaffe[3] take *the view that if the criteria of malignancy* that I have referred to earlier are fulfilled then the initial resection should be radical enough to avoid subsequent recurrence I think that the one exception to this is the chondroma of the hand which is usually benign

PROF ORR I would certainly agree with that

DR SPENCER Even so the cartilaginous tumors are often very pleomorphic In one and the same tumor one can find some areas that look benign and regular and others that show the more malignant features that are seen in the present case

PROF STUART HARRIS Have you any experience of tumors of this type arising in tissues other than bone? For example have you seen them arising from bronchial cartilage?

DR HEATH Well of course the common cartilaginous tumor of the bronchus is the adenochondroma but I think that we would all regard that as a very benign and quiescent tumor I have never personally had to deal with a malignant tumor of bronchial cartilage

PROF ORR Macroscopically the tumor of the right atrium in this case looked like a myxoma Dare I suggest that it is a myxoma?

*DR HEATH I do not think that it can* be for two reasons First the histopathology of the tumor is quite unlike that of a myxoma which we have already discussed in one of this series of conferences[4] The tumor cells here were definitely cartilaginous in type and did not resemble the stellate cells of the myxoma Second I have never heard of a myxoma of the right atrium giving rise to large metastases in

the lungs As you know there is a great deal of discussion in the literature about whether a myxoma ought to be considered to be a true neoplasm at all[4] I have personally seen only one case in which metastatic spread of a myxoma to the lungs was considered to have occurred and even in that case the invasion through the walls of the pulmonary blood vessels was very early indeed[5]

DR DAYLEY Well Professor Stuart Harris we congratulate you on getting so close to the diagnosis of this difficult case

*Diagnosis* Chondrosarcoma of the right atrium left lower lobe and peritoneal cavity in a woman with rheumatoid arthritis and previously resected chondroma of rib

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## Potentials and limitations of patients after myocardial infarction


*George E Burch M D**
*Nicholas P DePasquale M D*
*New Orleans La*


Although controversy still exists concerning the etiology of coronary heart disease it is a well accepted fact that by the time most American males reach 50 years of age they have some degree of coronary artery atherosclerosis Furthermore although the incidence of most other forms of heart disease has decreased in the last few decades the incidence of coronary heart disease has increased at least in the younger age groups At present coronary heart disease is probably the most common cause of chronic disability among the working population of the United States Furthermore about one third of all deaths in the United States each year are due to acute myocardial infarction

Patients with coronary heart disease may be divided into three groups on the basis of the clinical findings viz (1) those with coronary insufficiency (anginal syndrome) (2) those with myocardial infarction and (3) those with congestive heart failure A patient may progress from coronary insufficiency to myocardial infarction and congestive heart failure or may manifest any one or two of the three phases All of the above mentioned conditions are important causes of absenteeism in the male working population

The incidence of acute myocardial infarction in the general population is difficult to determine However it has been estimated that 1 out of every 38 men over 40 years of age and 1 out of every 115 women in the United States has an acute myocardial infarction each year[1] Although the mean age at the time of the initial myocardial infarction in white males is between 58 and 60 years the risk of myocardial infarction increases rapidly after 40 years of age It is during these years that many men reach their peak productivity and hold key positions in industry and the professions In addition many men in this age group are heads of households with large financial demands such as the education of children the payment of insurance premiums and mortgages etc The mortality rate of an initial myocardial infarction in patients between 45 and 60 years of age in many representative large series is about 40 per cent However in some series particularly those from private hospitals the mortality rate of initial myocardial infarction has been reported to be as low as 5 per cent Furthermore life expectancy in men who survive the first myocardial infarction is fairly good the average being about 10 years in patients who are less than 50 years old and 8 5 years in patients who are over 50 years old


From the Department of Medicine Tulane University School of Medicine and the Charity Hospital of Louisiana New Orleans La


This work was supported by grants from the United States Public Health Service the [illegible] Research in Heart Disease [illegible] Memorial Fund [illegible] Laboratory
Received for publication [illegible] 29 1966


*Address Department of Medicine Tulane University School of Medicine 1430 Tulane Ave New Orleans La 70112

at the time of the first infarction. Thus the physician will be faced with the problem of evaluating the capacity to work in at least 6 out of every 10 patients between 45 and 60 years of age who sustain an acute myocardial infarction. This is a difficult task which rests almost completely on the physician in charge of the patient. It is now well recognized that the majority of patients who survive an initial myocardial infarction can be returned to complete or partial employment. However, it should be stated at the outset that there are no rules, criteria, or tests for evaluating the work capacity of patients after a myocardial infarction which can be substituted for the physician's judgment. To be sure, certain tests of function may guide the physician, but the ultimate decision in regard to work capacity is one of clinical judgment rather than mathematically precise criteria.

*What is cardiac rehabilitation?* The term *rehabilitation* has many meanings. In the minds of most lay people and to many physicians, rehabilitation implies some form of physical training to regain or improve a loss of function resulting from disease, as, for example, various exercises in patients with cerebrovascular accidents or paralytic poliomyelitis. In patients with coronary heart disease, physical methods may assist the heart to function with the maximum efficiency possible for the anatomic state of the heart, but once this point is reached, cardiac function cannot be improved by training. There is little reliable information on the value of physical conditioning after myocardial infarction. Experimental studies in dogs have indicated that exercise promotes the development of the coronary collateral circulation after constriction of a coronary artery.[4] Nevertheless, a great deal more needs to be learned about the effect of physical training on cardiac performance in postmyocardial infarction patients before its role in the treatment of coronary heart disease can be evaluated.

Committees established to study the problems of rehabilitation of cardiac patients usually describe the aims of cardiac rehabilitation rather than define what rehabilitation means. These aims usually include restoring the patient's self reliance for the purpose of returning him to his former employment or, if that is impossible, to employment compatible with his working capacity.[5] Although these aims are essential to the long term management of patients after myocardial infarction, they do not constitute cardiac rehabilitation. In this regard, it is important to distinguish between cardiac rehabilitation and rehabilitation of the patient who has had a myocardial infarction. The aims listed above are directed toward rehabilitation of the patient rather than rehabilitation of the heart.

What then is cardiac rehabilitation? In our opinion, cardiac rehabilitation in the patient with coronary heart disease consists of the following: (1) preservation, as much as possible, of the structural integrity of the myocardium through adequate treatment; (2) institution of therapy directed toward establishing the greatest possible coronary collateral circulation; (3) institution of therapy directed toward encouraging compensatory myocardial hypertrophy.

The first two of these are the most important and apply to all patients with heart disease. The third applies primarily to patients with large dilated hearts. It is disturbing to us that so much of the literature on cardiac rehabilitation is concerned with getting the patient back to work, and that there is so little emphasis on preserving and improving the functional state of the cardiac muscle. In the final analysis, it is the efficiency of the heart as a pump which will determine the ability to work. It must never be forgotten that the motor of the pump is the myocardium itself. The efficiency of the heart after a myocardial infarction will be determined to a large extent by the adequacy of treatment. Once functional myocardial motor units are dead, they can never be regained. Thus, in so far as the heart is concerned, rehabilitation and treatment are to a great extent the same thing. Obviously, the effectiveness of physical training in improving cardiac efficiency will depend upon the amount of healthy myocardial tissue which exists after recovery from infarction. The potentials and limitations of patients after myocardial infarction are therefore greatly influenced by the treatment received during the period of infarction.

The three aspects of cardiac reh

tion outlined above are discussed briefly below.

*Preservation of the structural integrity of the myocardium.* After occlusion of a coronary artery, a variable amount of myocardial tissue is destroyed. This results in a loss of myocardial motor units so that there is impairment of the heart as a pump. The degree of impairment depends upon the amount of myocardial tissue lost, as well as losses accumulated previously from myocardial fibrosis associated with coronary artery disease, even in the absence of antecedent clinical myocardial infarction. During the early phases of myocardial infarction the area of injury and ischemia is greater than the ultimate area of death. Thus nonfunctioning but viable myocardial fibers regain their ability to function as a result of physicochemical reparative processes. Therapy should be directed toward insuring recovery of the maximum number of injured muscle fibers. Like any other organ, the diseased heart repairs and returns to good health most quickly when it is permitted to rest. Although the heart must continue to work even when it is diseased, it is possible within limits to "unload" and thereby rest the heart by means of relatively simple measures including (1) decreasing the heart rate, (2) decreasing the arterial blood pressure, (3) decreasing the cardiac output, (4) decreasing the size of the heart, and (5) decreasing the velocity of myocardial contraction. The physician should review each of these factors in terms of his patient in order to determine which apply to his patient and whether appropriate therapy to modify a given factor has been instituted.

In order to put the heart at rest, i.e., reduce the hemodynamic load to a minimum, it is not sufficient merely to put the patient with acute myocardial infarction to bed. It is also necessary to recognize and alleviate the psychic disturbances associated with the realization by the patient that he has had a myocardial infarction. This can usually be accomplished by calmness and reassurance on the part of the physician and the judicious use of sedatives. It is also important that the patient be placed in a thermally neutral and comfortable environment. A hot and humid environment increases cardiac work, so that even when the patient is at complete bed rest, the heart is not at rest. The importance of this factor is obvious to those who have observed patients with acute myocardial infarction treated during the summer months in hospitals that were not air conditioned. Careful attention must also be paid to such details as providing for small frequent feedings of soft, low residue foods, making certain that the patient does not develop bladder distention or fecal impaction, limiting the number of visitors and eliminating disturbing visitors, relieving pain promptly through the use of narcotics, and not allowing the patient to be disturbed by so-called "hospital routine," such as bathing the patient, changing bed linens, and the like. Complacency in the treatment of acute myocardial infarction has developed because of the fact that many patients survive an acute myocardial infarction no matter how they are treated. The point to be emphasized is that the goal of the treatment of acute myocardial infarction should be not only the survival of the patient, but also his recovery from the infarction with the least amount of myocardial damage. Many inadequately treated patients do survive, but they are often left with a dilated heart, congestive heart failure, and angina pectoris. This is not to say that adequately treated patients do not have these residuals, but only that they are less likely to occur in properly treated patients.

In our opinion, the single most important aspect of myocardial infarction in so far as prognosis is concerned is the size of the heart several months after an acute myocardial infarction. The patient who survives a myocardial infarction without developing cardiac enlargement can usually look forward to a productive and relatively symptom-free life. On the other hand, the patient who develops a dilated heart as a result of myocardial infarction is likely to be seriously incapacitated. The mechanical disadvantage of the dilated heart has been discussed previously in papers from this laboratory.[4,4] It is only necessary to emphasize the fact that whereas the tension in the wall of the normal-sized heart decreases or remains constant during systolic ejection, the tension in the dilated heart must increase to

support intraventricular pressure. Furthermore, for a given amount of work, the greater the myocardial tension, the greater the myocardial oxygen consumption and consequently the less the efficiency of the heart.

*Instituting therapy directed toward establishing the greatest possible collateral coronary circulation.* It is a well established clinical fact that patients with severe angina pectoris may in time experience a decrease in the severity and number of anginal attacks. Presumably, improvement is due to the development of the collateral coronary circulation. Furthermore, although it has not been established, it has been suggested that coronary vasodilators promote the formation of collateral vascular channels in the myocardium. Patients with severe angina pectoris should be treated with coronary vasodilators and their activity should be limited but not absolutely restricted. Limitation of activity is important if further myocardial damage is to be avoided. On the other hand, exercise may contribute to the development of the collateral circulation. Unfortunately, there are no criteria by which the physician can determine the amount of exercise that is appropriate for his patient. The amount of exercise prescribed must be based on judgment supported by the physical examination, the subjective response of the patient, and the electrocardiographic and roentgenographic findings. Cigarette smoking should be curtailed and completely eliminated if possible. It is probably also wise to restrict the use of caffeine-containing beverages. When an adequate collateral circulation develops, as is evidenced by a decrease in the frequency and severity of anginal episodes, the patient may increase his activity gradually. The fact that angina pectoris is a significant cause of absenteeism, as reported in so many studies on the work capacity of patients with coronary heart disease, indicates that present attitudes concerning the rehabilitation of cardiac patients need revision. In the long run it is better to delay the return to work of the patient with postinfarction angina pectoris until an adequate coronary collateral circulation has been established than to encourage too early a return to work. Although a patient with angina pectoris may be able to stay on the job, especially if he has a healthy psychologic approach toward his work, permanent disability and retirement may occur earlier than if employment had been delayed and activity restricted. The present aggressive attitude of those involved with the rehabilitation of cardiac patients is disturbing in that too often it appears that the major concern is with getting the patient back to work rather than with what happens to the patient after he returns to work. Nevertheless, the physician must temper his judgment with the realization that the longer the patient remains away from his job, the more difficult it becomes for him to return to work.

*Instituting therapy directed toward encouraging compensatory myocardial hypertrophy.* Patients with coronary heart disease, extensive myocardial damage, and massive cardiac dilatation represent one of the most frustrating problems to the cardiologist. Although patients with large dilated hearts cannot and should not work, the physician occasionally encounters such a patient who is strongly motivated to work. In some instances, because of the nature of the patient's work, for example, if he is a top executive or an artist, partial return to work may be possible under the physician's careful supervision. However, the vast majority of patients with extensive myocardial damage and large dilated hearts should not be permitted to work. Such patients often experience symptoms even at rest. Treatment in general consists of diuretics, digitalis, and low sodium diet. In addition, the physician is often called upon to treat acute episodes of cardiac asthma, pulmonary edema, or myocardial insufficiency. However, this therapy is only supportive, and the clinical course is one of progressive deterioration.

There is a pressing need to develop methods to improve cardiac function in patients with large dilated hearts. There is preliminary evidence to indicate that such patients may be improved by prolonged absolute bed rest.[7] Although the value of prolonged bed rest is well established in the treatment of tuberculosis and rheumatic fever, it has not generally been applied to patients with coronary heart disease. In fact, there is a tendency to en

courage patients with dilated hearts and chronic congestive heart failure to get out of bed because of an increased risk of thromboembolic disease It can only be said that the application of present therapeutic concepts have been largely unsuccessful *Unless new forms of treatment are* developed no improvement in the present gloomy outlook for patients with large dilated hearts can be expected Although placing patients with dilated hearts at absolute bed rest for a year or more is in some respects a drastic procedure the seriousness of the disease requires drastic measures The dilated heart is under a mechanical disadvantage when compared to the normal sized heart The tension developed by a given segment of myocardium during systole is related to the intraventricular pressure and the cross sectional area of the ventricle at the level of the segment[3,4] During systole the cross sectional area of the normal sized heart decreases so that the product of pressure times cross sectional area i e the tension in the myocardial segment either remains unchanged or may actually decrease Thus the normal sized heart is able to loaf during systole On the other hand the cross sectional area of the dilated heart does not decrease sufficiently during systole to prevent a marked increase in myocardial tension as systole progresses The increased tension which de*velops in the wall of the dilated heart im*poses an unfavorable load on the dilated heart This is a physiologic or static load because it is not associated with the movement of blood Furthermore the increased tension also imposes a metabolic load on the dilated heart because myocardial oxygen requirement is directly related to tension Prolonged bed rest is often associated with a decrease in cardiac dilatation Any decrease in the state of dilatation of the heart automatically unloads the heart to some extent Theoretically as the heart is unloaded improvement in myocardial function results in a further reduction in the dilated state which in turn results in further unloading of the heart and so on until the heart returns to normal size Of course this cycle is limited by the degree of myocardial damage However as collaterals develop or if one coronary artery is less narrowed than the other compensatory localized myocardial hypertrophy may develop in the areas that have a relatively good supply of blood We have described the hearts of patients in whom one coronary artery was occluded and the other was patent[8] *The myocardium in the dis*tribution of the occluded coronary artery was thin and fibrotic and in some instances dilated to the point of formation of an aneurysm On the other hand the myocardium in the distribution of the patent coronary artery was markedly hypertrophied It is reasonable to consider that placing a patient with coronary artery disease and a large dilated heart at complete prolonged bed rest by removing the static and metabolic load from the heart will encourage the gradual development of localized myocardial hypertrophy Of course the degree of hypertrophy will be limited by such factors as the extent to which each coronary artery is involved by the arteriosclerotic process and the effectiveness of the collateral coronary circulation

*Rehabilitation of the cardiac patient* As stated above it is important to distinguish between *rehabilitation of the heart* and *rehabilitation of the patient* with heart disease The determination of the potentials and limitations of patients with cardiac disease depends primarily upon the evaluation of the patient by *his physician It cannot be* done from tables charts or by boards of physicians It is unrealistic first to classify a patient in a certain therapeutic category and then to look up in a table how much and the kind of work he can do even when such tables are used only as guides Tables of energy expenditure during various tasks are subject to large errors especially when the task is not sedentary In fact under certain conditions it may be virtually impossible to estimate the metabolic cost of a complex task because of the variation in time spent at different phases of the tasks each phase requiring a different expenditure of energy Furthermore tables of energy expenditure provide information on the total metabolic cost of various activities they do not indicate the amount of cardiac work performed while carrying out these activities Nevertheless it is worth

while for the physician to acquaint himself with such tables of energy expenditure in order to get a general idea of the relative energy costs of various tasks (Fig 1)

The use of boards of physicians to determine work capacity is a poor practice No physician no matter how talented he is is able to evaluate accurately the work capacity of a patient on the basis of a single examination except perhaps that of patients who are so seriously ill that incapacity is obvious Members of such boards are usually aware of this fact and for this reason tend to rely heavily on functional tests of cardiac efficiency At present no test of cardiac efficiency can reliably predict the capacity of a patient to work When a physician bases his opinion of capacity to work on tests of cardiac efficiency he does the patient an injustice The physicians on some boards particularly those in state welfare departments never see the patient whom they are evaluating and therefore must base their decision on the physical examinations of other physicians and the comments of a social worker who in most instances they do not know personally The inadequacy of such a practice needs no comment

The decision of whether a patient is to return to work after a myocardial infarction as well as the time and type of work that he is to return to should be made only by the patient's physician This is a responsibility of which he cannot divest himself He may seek the help of a consultant or even a rehabilitation board but ultimately it is he who must make the final decision More attention should be paid to informing the practicing physician of the problems in the evaluation of the potentials and limitations of the patient who has had a myocardial infarction and less attention to educating the patient about his infarction Much of the literature prepared for lay people is filled with oversimplifications

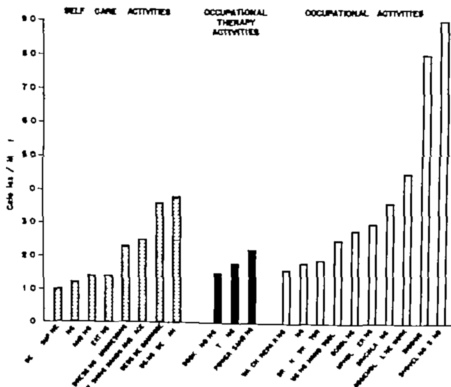



Fig 1 Average energy costs (in calories per minute) of various activities in man (Data from Purdue Farm Card Project and Henry Lyon and associates )

and half truths which confuse the patient. The patient's best source of information is his own physician, not paperback books and brochures.

During the early period of treatment of an acute myocardial infarction the physician will continuously evaluate the severity of the infarct and the response of the patient. He will also evaluate the psychologic effect of the infarction on the patient and his family. As the patient improves, he will be gradually allowed to increase his activity until he becomes fully ambulatory. There is no timetable for determining the period of bed rest, sitting in a chair, and finally ambulation. However, it is better to proceed too slowly than too rapidly. During this period the physician will encourage the patient and his family so that when the patient is ready to return to work he will have a good mental outlook. But the physician must be careful. It is just as important for the patient to know his *limitations* as his *potentials*. The physician will observe the response of the patient to a progressive increase in activity. On the basis of the physician's impressions and the patient's symptoms as activity is increased, the activity will be adjusted to the patient's capacity. Eventually, a sound judgment in regard to work capacity will be reached. This judgment will be based on observations and impressions formed during the entire period of treatment and convalescence. It will include not only the consideration of the patient but that of his family, his employer, and his supervisors, his attitude toward his job and the job itself, as well as many intangibles. A judgment in regard to the potentials and limitations of a patient after a myocardial infarction that is made on any other basis is an unsatisfactory compromise.

## Conclusion

At present it appears that about 80 per cent of patients who survive an initial myocardial infarction are able to return to work (Fig. 2). However, among such patients absenteeism due to angina pectoris, congestive heart failure, and cardiac asthma is relatively frequent. In Dimond's study of 348 patients who returned to work after an initial myocardial infarction, 25

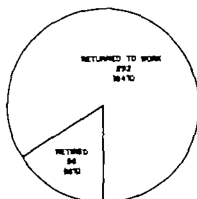



Fig. 2. Fate of 348 men who survived initial myocardial infarction and returned to work. (Data from Dimond.[3])

per cent sustained a second myocardial infarction within 5 years.[3] Thus, although every effort should be made to have patients return to work after a myocardial infarction, the physician must recognize the risks of returning to work too soon as well as the advantages and disadvantages of prolonged inactivity. Until morbidity is reduced, management will continue to be reluctant to employ men who have had a myocardial infarction, particularly for relatively unskilled tasks. The best means of reducing morbidity is adequate treatment during the acute and convalescent phases of the period of myocardial infarction.

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# Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Alan F Lyon

## Reappraisal of digitalis Part IV
## Metabolism of the cardiac glycosides


*Alan F Lyon M D**
*Arthur C DeGraff M D***
*New York N Y*


There are two major reasons why the use of digitalis remains empirical The first concerning the uncertainty of its precise physiologic effects has already been reviewed in this series The second reason is incomplete knowledge of its absorption distribution metabolism and excretion Although there is information concerning a few glycosides in a few animal species differences between glycosides differing responses to the same glycosides in different species and differing responses even in different individuals of the same species are known to exist and cannot be adequately explained The lack of detailed information despite much ingenious and tedious investigation is due to the difficulty in the identification of the digitalis glycosides and their metabolites in tissue The total amount of any glycoside in therapeutic dosage in the body at any time is very small and most of this is fixed to tissue The quantities of digitalis in the blood are therefore infinitesimal and blood levels are of little value in the study of its metabolism Since digitalis glycosides are steroid compounds quite similar to many natural substances in the body chemical separation is difficult Although there are a number of reagents both acidic and basic which combine with the digitalis glycosides and allow precise quantitative determination none of these is unaffected by other tissue substances and they cannot be used for direct assay in biological systems On the other hand bioassay can be accomplished by measuring the effect of a test substance on contractility of cat papillary muscle or on the cardiac rhythm of chick or duck embryo Finally isotope assay has been accomplished with two glycosides digitoxin and digoxin Digitoxin has been prepared as the $C^{14}$ isotope by isolation from the plant *Digitalis purpurea* grown in an atmosphere containing $C^{14}O_2$ Digoxin is available in the tritiated form that is with tritium substituted for hydrogen Both the bioassays and isotope assays are extremely sensitive but cannot be used on unprepared tissue samples because of the interference or the toxicity of other substances in the case of the bioassays and because of uncertainty about the persistence of the isotope tag on a cardioactive glycoside in the case of the isotope assays Therefore in all cases the tissue sample whether blood urine or tissue homogenate must first be prepared by some kind of separation usually chromatographic using one or more of the chemical reagents mentioned above and then


Received for publication on Sept 19 1966


*Chief Cardiology Sect Veterans Administration Hospital [illegible] N Y
**Professor of Therapeutics New York University College of Medicine [illegible] Veterans Administration Hospital [illegible] N Y

elution and measurement A tremendous amount of work is involved in such studies *hence only limited data are available* Although these data agree in trend there are many presently unreconciled discrepancies in the results obtained by various assay methods Therefore only an outline of the metabolism of the digitalis glycosides can be presented at this time with any degree of reliability

There is a marked difference in the metabolism of the clinically used cardiac glycosides depending on their degree of polarity or water solubility Digitoxin is the most studied example of the relatively nonpolar nonwater soluble lipid soluble glycosides ouabain at the other extreme is more polar less lipid soluble and more water soluble Intermediate between these compounds is digoxin on which a fair amount of information is available

It is generally agreed that digitoxin is almost completely absorbed from the gastrointestinal tract Ouabain and lanatoside C are poorly absorbed presumably because they are less lipid soluble Another factor that may be operating to interfere with gastrointestinal absorption of many *of the* strophanthus group and of gitoxin is the destruction of the drugs in the gastrointestinal tract because of greater susceptibility to gastrointestinal enzymes

Information about the absorption of digoxin is less clear Prior to the availability of isotope assay there were various clinical studies some of which showed digoxin to be equally potent orally and intravenously and others which seemed to show as much as a 2 1 difference Studies of tritiated digoxin show that about 90 per cent of digoxin is absorbed but that 20 per cent can be recovered from the stool the additional 10 per cent resulting from biliary excretion In one patient who required a large amount of digoxin clinically 35 per cent of a single dose was found in the stool Whether this was due to decreased absorption or increased biliary excretion i not known Such individual variation may account for the discrepancies in previous clinical studies

Once absorbed into the circulation all digitalis preparations are widely distributed through the body and rapidly fixed to tissue Nearly complete disappearance from the blood is rapid The concentration of labeled *digitoxin given intravenously* has been reported to fall to 12 per cent of the initial level at 15 minutes and to less than 5 per cent at 3 hours Tritiated digoxin given in a single dose intravenously falls to 10 per cent of the initial level after 3 minutes and to 2 8 per cent at 1 hour The more polar short acting glycosides have not been identified one half hour after a single dose With the use of precise techniques a small amount of digoxin continues to be found in the serum with a half life of 23 hours This is at a very low level one fortieth of the tissue concentration but appears to be in equilibrium with it Small amounts of digitoxin are more easily identifiable in the serum and persist for even longer times This is due to protein binding probably to albumin and may be an important factor in the long duration of action of digitoxin

The distribution of digitalis glycosides to tissues is fairly uniform and does not show any predilection for cardiac muscle If anything higher concentrations are recorded in the liver and organs of excretion $C^{14}$ digitoxin concentration *in the* heart has been found to be from 0 5 to 2 times $10^{-8}$ molar A partial blood brain barrier to distribution has been demonstrated at least for digoxin

The fate of the various digitalis glycosides varies widely The more polar and clinically shorter acting ouabain and lanatoside C are excreted rapidly through the bile It has been reported that 83 to 93 per cent of a single intravenous dose of ouabain and 60 to 85 per cent of a similar dose of lanatoside C could be identified in the bile 5 hours after administration At the opposite extreme is digitoxin which persists for a long time in the body both as unchanged digitoxin (with a half life of 9 days) and as cardioactive metabolites About 70 per cent of digitoxin is metabolized prior to excretion A considerable portion of this is via hydroxylation to compound C which has now been identified to be digoxin Another metabolite not yet identified is called compound C It is identical to compound B formed from administered digoxin About 70

cent of digitoxin and its metabolites can be recovered from the urine about 20 per cent in the first 3 days and the rest over a period of 40 days About 10 per cent of digitoxin is excreted in the bile some of this is probably reabsorbed but some appears in the stool Further evidence of the long duration of digitoxin in the body is the persistence of S T segment and T wave abnormalities in the post exercise electrocardiogram of some normal subjects for up to 6 weeks after a single dose of digitoxin

Digoxin is intermediate in rate of excretion and metabolic degradation Only about 5 to 10 per cent of digoxin is transformed prior to excretion Unlike digitoxin which is probably degraded in the liver the metabolic alteration of digoxin takes place primarily in extrahepatic sites The biologic half life of digoxin is only 1 5 days About 80 per cent of an intravenous dose is finally excreted in the urine and the remainder in the stool Thirty seven per cent of a single dose has been reported to be excreted in the urine in the first 3 days and essentially all is excreted in 10 days This correlates with the electrocardiographic findings that S T segment and T wave abnormalities persist in the post exercise electrocardiogram for only 4 days after a single dose of digoxin

Clinical importance is attached to the effect of three conditions on the metabolism of digitalis glycosides these are uremia severe liver disease and cardiopulmonary bypass In each instance the present evidence is either fragmentary or to some extent contradictory In the case of uremia it would appear at least in the case of digoxin that patients with severe renal insufficiency have a reduced rate of excretion On the basis of these data with some extrapolation it has been suggested that in patients with blood urea nitrogen of 50 mg per cent or more the maintenance dose of digoxin be reduced to one half or one third of the usual dose There is no information on the effect of renal insufficiency on the initial loading doses Studies with tritiated digoxin in patients having hepatic insufficiency have shown no change in the rate of its excretion in the urine or feces or in the partition of metabolites On the other hand animal studies employing partial hepatectomy showed slow disappearance of ouabain because of interference with excretion and slow disappearance of digitoxin because of slower degradation The clinical significance of these observations is not clear The effect of cardiopulmonary bypass on stores of digitalis is also uncertain It has been shown that no significant amount of digitalis is removed by hemodialysis in uremic patients Investigators differ about the effect of cardiopulmonary bypass with reports of either no significant change or a modest loss of digitalis The problem is further complicated by the observation that tritiated digoxin is handled differently from the normal in the post bypass state *with a faster turnover initially and then* slower turnover

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# Annotations

## Cardiac transplantation without complete cardiac denervation

### The role of the afferent receptors

It has been assumed by most authors that total denervation of the heart is an una oidable conse quence of cardiac transplantation It is the intent of this brief review to emphasize that cardiac trans plantation can be performed in such a way that major afferent receptors in the heart are preserved These receptors may play a ital role in maintaining stability of the circulation in the recipient of the heart tran plant

Considerable ev dence has now accumulated to indicate that the posterior atrial wall particularly at the atrial-caval junctions and the ostia of the pulmonary sinus richly supplied with baroreceptor end organs The e receptors appear to play a significant role in maintaining circulatory homeostasis and fluid volume control by means of neuro endocrine reflexes The evidence suggests that small changes in intrathoracic blood olume are readily detected by strategic receptors in the atria which transmit vagal impul es to reflexly influence ADH secretion Other tudies have revealed relationship between atrial timulation and adrenal cortex secretion As a result of such neuroendo crine reflexes renal and possibly cardiac compen tory mechanisms maintain more stable circulatory state These volume control mechani ms ha been comprehensively reviewed by Gauer nd Henry

One metho l of cardiac transplantation in the dog previously described [10] employs transection of donor and ecip ent hearts at the level of the atria leaving inta t the entire posterior atrial wall in the recip ent an mal ncluding a ridge of trial eptum This technique as originally selected as a means for mo rap d anastomot c restorat on of enous inflow It now recognized that a more important result may be the preservat on of volume receptor afferent nerve supply This feat may to a large extent explain discrepancies in the ob served incidence of cardiac failure in the postopera tiv state after cardiac transplantation reported by various investigat W llman and associates early demonstrate l the fea bility of survival after total cardiac dener ation an l after cardiac auto tran plantat on \ erthele they frequently ob served the retent on of flu d nd other man festa t ons of cardiac fa lure in the postoperative period These observations were striking contrast to those of our own group that man festations of card ac fa lure were rare The major difference in operati e technique which may explain this discrepancy the more complete preservation of afferent receptors by the method which leaves in tact the posterior trial wall

Further testing of this hypothesis should be of the utmost importance in selecting the appropriate technique for cardiac tran plantation Cognizance of the role of card ac afferent receptor may be of equal mportance to those designing and investi gating the mechanical heart

*Richard R Lower M D*
*Associate P ofessor and Chairman*
*Divi ion of Thoracic and Ca diac Surgery*
*Medical College of Virginia*
*Richmond Va 23219*

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# Fresh nitroglycerin (glyceryl trinitrate)

The controversy over the mechanism of action of nitroglycerin should not be interpreted as an argument over the effectiveness of the drug in the treatment of angina pectoris. Regardless of the mechanism whereby nitroglycerin relieves the pain of coronary ischemia, in our opinion there is little doubt that it does so. Not only should nitroglycerin be readily available to all patients with coronary heart disease in the event of an episode of angina pectoris, but the physician should also recommend its use in prophylaxis. For example, patients should be advised to place nitroglycerin under the tongue before eating or sexual intercourse if these activities frequently precipitate an attack of angina pectoris. It is sometimes forgotten that nitroglycerin is useful in the diagnosis of coronary heart disease. When there is doubt whether a patient is experiencing angina pectoris, the response to nitroglycerin will often provide the diagnosis.

Nitroglycerin is inactivated by time, light, heat, air, and moisture. When a patient reports that nitroglycerin failed to relieve an episode of angina pectoris, it should be suspected that the nitroglycerin was inactive. We have many times observed patients, some of them physicians, who carry nitroglycerin which is many months or even years old in a clear bottle with a metal cap or in a metal pill box. Some patients keep nitroglycerin in the glove compartment of their car where it is subjected to intense heat during the warm months of the year. Patients frequently keep nitroglycerin in an inside pocket where the heat of the body speeds up the deterioration of the drug. Nitroglycerin often stands on the druggist's shelf for many months before it is finally dispensed. Under such circumstances the concentration of nitroglycerin in each tablet is unknown. However, it is certain that it is less than the dose prescribed by the physician. The mere fact that the label on the bottle indicates 1/200 grain of nitroglycerin guarantees only that the manufacturer placed that much nitroglycerin in each tablet; it does not guarantee that the patient placed 1/200 grain of nitroglycerin under his tongue.

Although many of these facts may appear to be elementary, we are disturbed by the number of patients with coronary heart disease who have not been instructed in the proper handling of nitroglycerin. The responsibility of advising patients on the proper care of nitroglycerin rests on the physician. If more physicians discharged this responsibility, perhaps there would be less discussion about the effectiveness of nitroglycerin in the treatment of angina pectoris. There are so few really effective drugs for the treatment of angina pectoris that patients or physicians must take full advantage of the therapeutic properties of nitroglycerin. Patients should be advised to purchase fresh nitroglycerin (the pharmacist can arrange this). The drug should then be placed in the refrigerator with the exception of a 1 or 2 week supply, which is placed in a dark bottle or a plastic container. Before additional nitroglycerin is removed from the refrigerator, the bottle should be allowed to warm to room temperature to avoid condensation of water on cold tablets. The nitroglycerin should be carried in a dark bottle or a plastic container and should not be kept close to the body. The tablets should not be stuffed down with cotton but should be kept in such a manner that the patient can remove them quickly from the bottle.

Nitroglycerin may be a life-saving drug. It should be treated as such by physicians and patients alike. An episode of angina pectoris may precipitate a fatal arrhythmia or a myocardial infarction. It is a tragedy when nitroglycerin fails to relieve such an episode of angina pectoris because it is inacti

*George E. Burch, M.D.*
*Nicholas P. DePasquale, M.D.*
*Department of Medicine*
*Tulane University School of Medicine*
*1430 Tulane Ave.*
*New Orleans, La. 70112*

# Methysergide and retroperitoneal fibrosis

For the past 5 years methysergide has been used in the management of migraine and other vascular headache; more recently it has also been used in the carcinoid syndrome[2] and postgastrectomy states. Side effects are common but usually mild and transient. Occasionally patients have developed arterial vasoconstriction and peripheral ischemia, usually self-limited but at times requiring surgical intervention.[4] Recently, more alarming side effects have been ascribed to methysergide therapy. These include retroperitoneal fibrosis and, more rarely, valvular lesions of the heart and pulmonary inflammation with fibrosis.[7]

Retroperitoneal fibrosis, first described by Ormond[8] in 1948, is an uncommon condition in which the ureters and other retroperitoneal structures become encased in masses of dense fibrous tissue. Early symptoms are nonspecific but may include discomfort in the abdomen or back.[10] Later the patient may become uremic. Anuria sometimes of sudden onset may occur, but uremia may be present despite an adequate volume of urine. Since obstructive uropathy is one of the few reversible causes of uremia, this possibility should not be overlooked and should be searched for in all cases of renal failure, acute or chronic. The diagnosis of retroperitoneal fibrosis is suggested when hydronephrosis and medial deviation of the ureter are seen by intravenous pyelography. This is confirmed by retrograde studies. Frequently, ureteral catheterization discloses no obstruction and the diagnosis only becomes apparent after dye is injected and the catheter removed. The fibrotic process may also involve other retroperitoneal structures, in particular the aorta and its large branches; venous obstruction is not uncommon in advanced cases.

The etiology is unknown. A relation hip to other sclerosing conditions such as mediastinal fibrosis, sclerosing cholangitis, Riedel struma, Peyronie disease, and Dupuytren's contracture is possible and the finding of one of these diseases should lead to a search for the presence of others.[14] Certain resemblances to the Weber-Christian syndrome suggest that the process originates as an inflammatory disease of adipose tissue.[15] An autoimmune mechanism and relationship to systemic lupus erythematosus and other collagen diseases has been postulated because of possible precipitation by hydralazine and occasional association with a hypersensitivity vasculitis. In some patients necrotizing arterial lesions have been found within the fibrous tissue.

A direct causal relationship between methysergide and the development of retroperitoneal fibrosis has not been proved. Nevertheless, the incidence of this rare disease has increased in recent years. Graham recently reported 27 cases of retroperitoneal fibrosis in patients treated with methysergide; spontaneous remission occurred in all cases after cessation of therapy, which suggests that such a development can hardly be fortuitous.[18]

The mode of action of methysergide is not clearly understood but may involve antagonism of serotonin or neurokinin, a peripheral action on blood vessels, or perhaps a central hypothalamic effect.[1] Methysergide apparently has no direct vasoconstrictor effect but can potentiate endogenous and exogenous vasoconstrictor substances such as catecholamines, nicotine, and ergotamine. Patients who suffer from migraine have a generally increased vascular response to vasoconstricting stimuli.[19] Since these patients also frequently take ergot preparations, a synergistic action may occur.

Spontaneous remission has so far occurred in all patients in whom treatment with methysergide was stopped. However, we have recently observed a patient in whom the condition appeared to develop or progress over a period of 6 months after cessation of therapy. It may well be that in susceptible subjects methysergide triggers a process which becomes self-perpetuating.

In view of these developments, we would suggest the following approach to the patient with retroperitoneal fibrosis when methysergide is incriminated. Formerly many patients were subjected to early surgical correction. We may now expect that spontaneous regression will occur in most cases after withdrawal of the drug. In addition, treatment with steroids may be of benefit in arresting the fibrosing process. Periodic follow-up examination is essential, however, because the process may progress and ultimately require surgical intervention.

Furthermore, we suggest that methysergide be used with great caution. Graham recommends that the drug should be avoided in patients with cardiovascular disease as well as in pregnant patients and those with liver and renal disease, connective tissue disorders, and a collagen-disease diathesis. Treatment should be intermittent rather than continuous, and periodic physical examination and assessments of renal function should be made. At this time the comment of A. L. Lipmark is quite appropriate: Although migraine is not usually regarded as a fatal disease, it may be a real danger to life, at least by means of iatrogenic activities.

Franklin D. Schwartz, M.D.
George Dunea, M.B., M.R.C.P., M.R.C.P.E.
Robert M. Kark, F.R.C.P., F.A.C.P.
Department of Medicine
University of Illinois College of Medicine
and Presbyterian–St. Luke's Hospital
1753 West Congress Parkway
Chicago, Ill. 60612

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# Research equipment for use in technically developing regions

The phys an equ pping him lf for research in solving lectrocard ar phy in a technically de veloping region should be as w ll sufficient as possi ble He would do well t take along a new portable battery run tran istorized electroc rdiograph unit and a supply of batteries chart roll and electrode jelly appropri t for that unit

A generalized fl ttening and dw rfing of com plexes in African children w re repe tedly noted in mains instrument recording t ken in medical units in both East and W t Afric At first the tracings were thought to refl t severe myocardi l and/or pericardial damage po ibly due to one of the problems common to the tropics electrolytic im balance protein-calorie m lnutrition tuberculo is chronic anemia and endomyocardi l fibrosis How ever well nouri hed vigorous y ung ters with congenital lesions such a patent ductus arteriosus and ventricular septal defect had relatively flat tracings A battery run unit the C mbridge Trans rite III w obtained and comparative trac ngs were made u ing a ingle set of electr des connected first to the main instrument and then to the bat tery run unit Tracings from the main instrument w re consi tently more flattened and dw rf d than tho e from the battery run unit It i l lieved that the cau for the low r mplitude of the complexes in the tracing from the mains instrument might have been due to low input impe lance

The possibil ty of l w impe lance in older equip ment the lack of suitable m ins in some l cations the unpredict bil ty of the lectrical power supply and the difficult terr n mak an easily port bl battery run model e pecially attractive and prob ably e ntial f r re arch in technically developing regions

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J an I Cidlell M D
Dep t ent of Pharmacology
George Washington University
1339 H St N W
Washington D C

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